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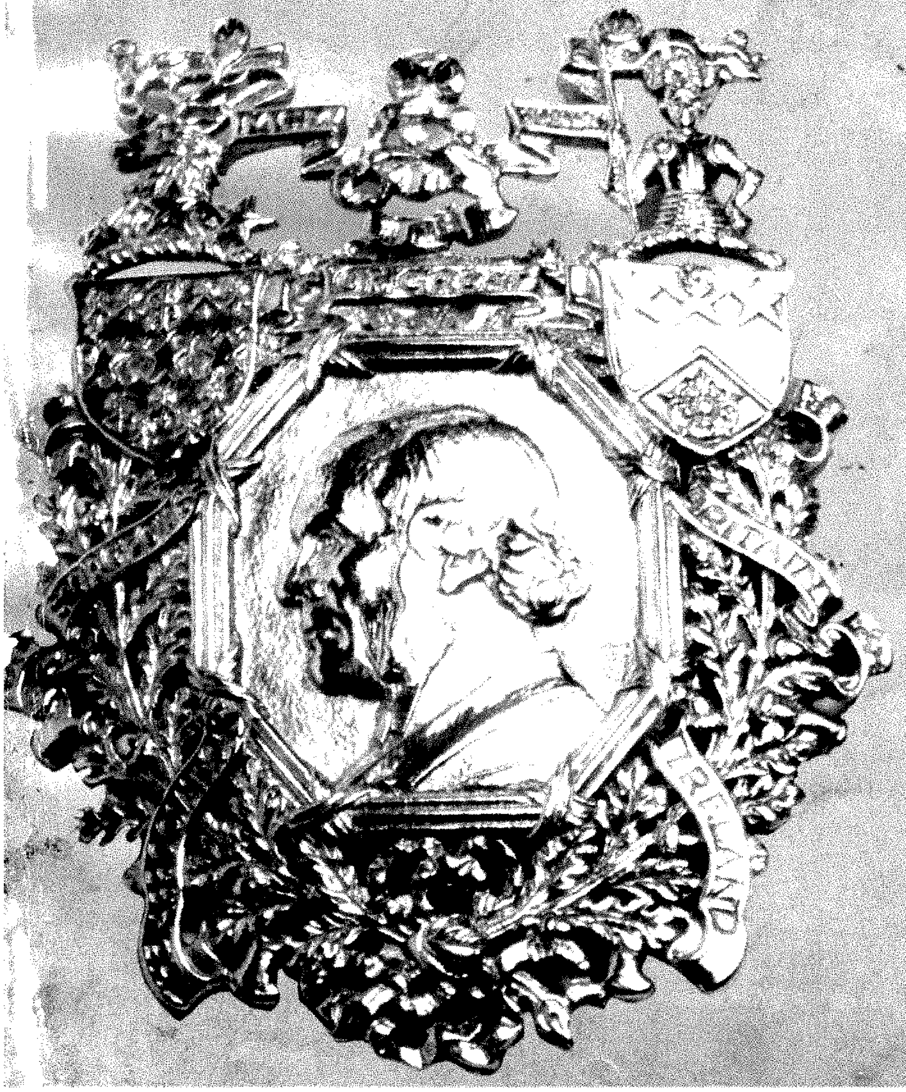

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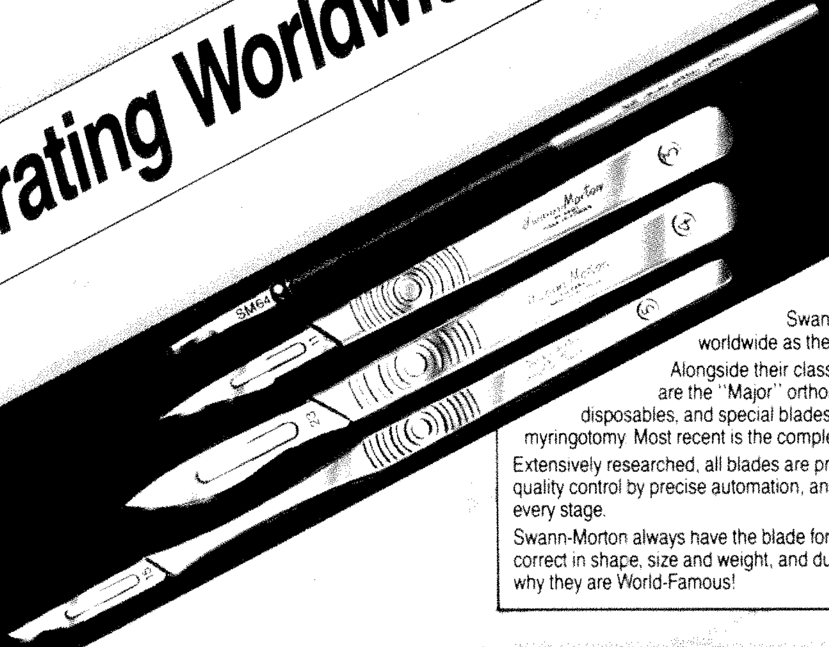

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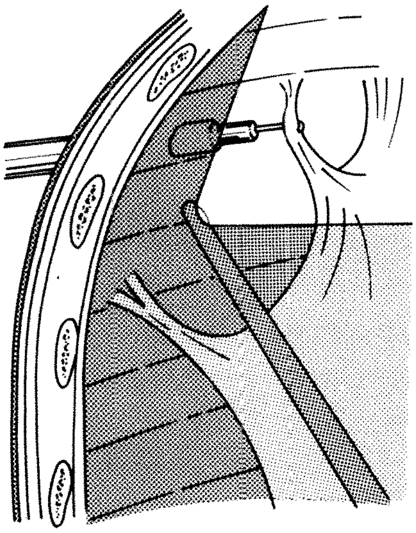

C. Boutin, J. R. Viallat, Marseille;
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Foreword by R. W. Light

1991. Approx. 176 pp. 119 figs. Hardcover DM 198,– ISBN 3-540-52369-3

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The editors approach the problem of critical leg ischaemia from a multidisciplinary viewpoint, and individual chapters concerning aspects of the pathophysiology and clinical management of this condition are written by experts in the field.

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J. Steffens, M. Ziegler, University of Homburg

Surgical Observations and Their Consequences

Vorgelegt in der Sitzung vom 18. November 1989

1990. 17 pp. 6 figs. 3 tabs. (Sitzungsberichte der Heidelberger Akademie der Wissenschaften. Jahrgang 1990. 3. Abh.) Softcover DM 15,– ISBN 3-540-52363-4

Contents: *F. Linder:* Accidental Hypothermia. – *F. Linder, J. Steffens, M. Ziegler:* Renin-Secreting Tumors of the Kidney with Secondary Hypertension.

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Operative Technique in Neonates and Infants

1990. VIII, 141 pp. 77 figs., some in color. 34 tabs. (Progress in Pediatric Surgery, Vol. 25) Hardcover DM 176,–
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1990. XI, 251 pp. Hardcover DM 180,–
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The cover shows the Presidential badge of the Association

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1. Planes A et al. Thrombosis and Haemostasis 1988; **60** (3): 407-410.

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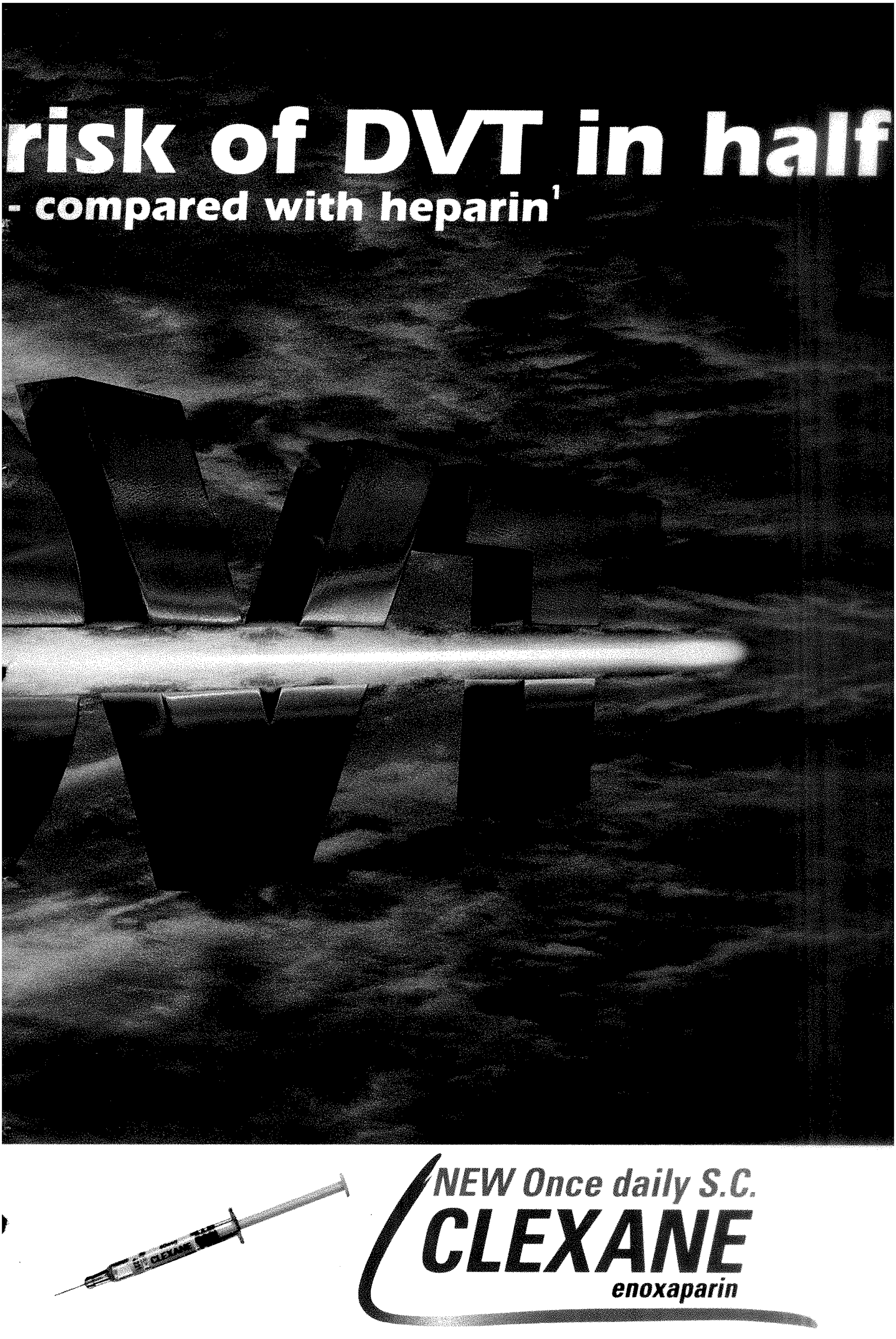

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Educate the phagocyte!

'Stimulate the phagocyte', cried George Bernard Shaw when expounding on his theories of disease prevention. During his era infection was rampant, blood transfusion unthinkable and antibiotics unavailable. Physicians and surgeons were faced with staggering mortality rates. The fields of immunology and infection control were in their infancy and the function of the phagocyte ill defined and mysterious.

In the light of recent studies, Shaw's judgement would on the surface appear to have been sound, if not prophetic. 'Phagocytes' or white blood cells of the monocyte lineage, are now known to have extraordinary potential to deal with invading organisms. In addition to their ability to engulf or phagocytose bacteria, they produce powerful enzymes to assist in digestion of these organisms, highly reactive metabolic by-products of molecular oxygen (oxygen free radicals) capable of destroying organisms, and elaborate metabolic mediators such as tumor necrosis factor (TNF) and interleukin-1 (IL-1). These substances in turn inhibit anabolic function and make available large quantities of carbohydrate and amino acids for immediate utilization under conditions of stress[1–3]. Such characteristics testify to a highly developed and efficient defence system designed for the protection of the patient threatened with pathogenic bacteria or a stressful encounter.

Times have changed, however, since Shaw's prophesy. With the dawn of the antibiotic era, infection is no longer the threat it used to be. Blood transfusion is readily available and electrolyte and nutritional therapy are a reality. Mortality rates from sepsis and blood loss have dropped and radical surgery can be performed with relative ease and safety. Patients who would have succumbed in Shaw's time as a result of infection, blood and fluid loss or lack of nutritional support, are now however, at risk of mortality from a new breed of phenomena. The sequelae of major blood and fluid replacement, extensive surgery, multiple trauma and major burns pose a considerable threat to patients treated in modern intensive care units. Complications such as adult respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), multiple organ failure, pancreatitis and prolonged refractory catabolic illness account for many late deaths[4,5].

Recent research indicates that substances produced by activated white cells may contribute much to patient morbidity and mortality. Oxygen free radicals, effective at eradicating many strains of bacteria, have been suggested to cause pancreatitis, ARDS, stress-induced gastric ulceration, and reperfusion injury in bowel, heart and kidney[6–8]. Moreover, the monocyte products IL-1 and TNF, efficient at mobilizing body substrate in the acute phase response to injury[1,2], are now thought to account for prolonged morbidity, hypermetabolism and significant mortality in cancer, burns, trauma, and infection[1–3,9,10]. Even the frequent complications of critical illness, Gram-negative sepsis and endotoxaemia, appear to cause metabolic and neurohormonal perturbations by elaboration of monokines[3,10], not by the direct effects of bacteria or their endotoxins as previously thought. The irony therefore is that cells of our defence system appear to cause significant morbidity in their efforts to defend against critical disease.

At first glance, phagocyte activation and stimulation of the acute phase response to injury and sepsis seems to be a beneficial response. Elimination of bacteria and tumour cells by radicals and mediators is highly desirable, particularly if no other form of therapy is available. The onset of tachycardia, the conservation of body fluids and sodium, and the mobilization of skeletal muscle protein would add to the ability of the host to respond to injury in a positive fashion. In the short term, these adaptations would be useful but in the long term their prolongation might lead to host self destruction. In times past, this situation would not have developed as without antibiotic therapy, nutritional support and intensive care facilities, patients with critical illness would have died within a very short period. Thus, in only the last few decades has prolonged survival uncovered the potentially deleterious side effects of monocyte activation. The high fever of infection, the tachycardia and the acute phase protein response to surgery are of dubious benefit now that fluid replacement, antibiotic therapy and aseptic techniques are available routinely. The time has come to question whether our immune system is acting in our best interests or whether indeed it has 'lost direction'.

According to the theory of natural selection, organisms most adept at survival should propagate while those whose defence systems are ineffective should perish. It may be that the time scale of nature's adaptability to environmental change has been outpaced by scientific development. Without recent advances in medicine, nature would naturally expect those undergoing major surgery to be at risk from blood loss, massive influx of pathogenic bacteria, substantial fluid depletion and prolonged lack of nutrition. An appropriate reaction for the immune system under such conditions might be to stimulate 'defence' cells to effect volume conservation, substrate mobilization and bacterial killing. These 'anxieties' of nature are now largely without foundation as modern medicine is equipped to

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cater for the majority of surgical complications. It is the side effects of immune cell activation which now complicate the outcome of the critically ill patient.

Is it possible to manipulate our immune system into behaviour where its now 'misguided' responses might be quelled to advantage? Experiments in the field of transplantation suggest that under stringent supervision and with the careful use of immunosuppressive agents specifically to suppress certain aspects of immune function, patients may fare well when receiving a foreign organ transplant. This is a situation where nature, unaided, would have obvious difficulties given that natural selection has developed to encourage rejection of foreign protein by the immune system.

Medical science was quick to recognize the need to manipulate the immune system when transplantation became technically feasible, but has been slow to accept that the system may be a little 'misguided' when it comes to the defence of the patient requiring prolonged critical care following major surgery or trauma. However, positive steps have recently been taken against some of the principal monocyte produced mediators of morbidity such as TNF and oxygen derived free radicals. Anti-TNF antibodies have been used to reduce mortality rates associated with experimental sepsis[10] and free radical scavengers have shown potential in experimental studies of pancreatitis and reperfusion injury[6,7]. Such experiments, which have only focused on single aspects of monocyte over-activity, indicate the vast potential of phagocyte regulation in critical illness.

One possible explanation for our failure to recognize that the immune system may be acting to the patient's detriment may be the use of the label 'immunosuppression' in many critically ill patients. It should be pointed out that the label is generally used to refer to specific changes in the immune system such as impairment of cell mediated immunity. It is often taught that in conditions such as AIDS, cancer, multiple trauma and sepsis, cell mediated immunosuppression occurs. Yet, in patients with these conditions, there is now definite evidence for exaggerated production of monokines such as TNF, IL-1 and prostaglandins, all of which are markers of excessive monocyte activity[1–3,9–11]. The term immunosuppression is therefore misleading and specific terminology should now be employed to detail the exact nature of immune deficit.

Thus, it appears that the efforts of the immune system on our behalf may be a little outdated and that Shaw's enlightened prophesy has run its course. It is not the fault of our immune system that its activity now poses a considerable threat to the critically ill. A system of defence evolving over millions of years in the best interests of our species could hardly have predicted that we could now replace one heart with another under aseptic techniques while maintaining tissue oxygenation with a machine and replacing blood volume with donations from volunteers of diverse phenotype. On the contrary, the 'blame' must lie with physicians who protest when such patients suffer the consequences of oxygen radical mediated reperfusion injury or monokine induced catabolic responses. After all, these reactions are thought by the simple phagocyte to be in the best interest of self preservation. It must also be remembered that the individual phagocyte is a poor student and is ill equipped to learn from past experience. The lymphocyte population can adapt over an individual's lifetime and, in consequence, can be sensitized to produce selected specific immunoglobulins, desensitized to a non-reactive state, or stimulated to clone specialized T-cells. In contrast, the humble phagocyte 'gives its all' when host survival is thought to be threatened.

'Educate the phagocyte' might be a more appropriate cry for future literary prophets.

D. B. Gough

Department of Surgery
University College Hospital
Galway
Ireland

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The dog in the night time

'May I call your attention to the singular incident of the dog in the night time?', said Sherlock Holmes. 'But the dog did nothing in the night time', said Dr Watson. 'That', said Holmes, 'is the singular incident'.

Could the HIV virus in the operating theatre be like that dog? For eight years surgeons have been awaiting with dread the loud 'bark' of evidence that our lives will henceforth be dominated by the risk of transmitting HIV either to ourselves or our patients. The welcome silence has recently been threatened by a clamour in the media for the testing of surgeons. This follows an American woman's allegation that she had contracted AIDS from her dentist – an assertion which appears to be supported by DNA sequencing, correlates poorly with our knowledge of the incubation period[1], and awaits further elucidation from the tracing of 500 other patients. What more popular vote catcher than, 'Your surgeon owes it to you to test himself regularly to protect you ...?'.

The mirror image of such plausible thought processes is already well established in the minds of many surgeons. Most of these have little experience of AIDS but are all too well aware of the frequency with which they breach their gloves or even their skin during operative procedures: 'Why should I place myself and my family at risk ... all patients should be tested!' Reluctance or even refusal to operate on patients known to be HIV-positive or in recognised risk groups is now widespread in the profession. Indeed the feeling that the act of surgery lies at the pivotal point of an incipient pandemic is gaining ground each month.

Whether or not the disease of AIDS is to dominate the future of our planet the position of surgery and invasive medicine within this cataclysm needs careful evaluation. When one considers the key role of blood and body fluids the sum of evidence is surprising. It has recently been reinforced by one remarkable study from Nashville, Tennessee, which is likely to be the most comprehensive that we shall see for some time[2]. It was made possible by the willingness of a surgeon who died of AIDS to make his diagnosis a matter of public knowledge and of three hospitals to co-operate in tracking down patients operated upon by him during his last seven years. During most of this time he was unaware of the diagnosis. None of 2160 patients traced has developed the disease and only one of 616 who were tested was HIV-positive. This patient's disease had almost certainly antedated the operation since he already had extra pulmonary tuberculosis, was a known intravenous drug abuser and a regular consort of prostitutes. In two previous, far less comprehensive, studies the negativity rate of patients of surgeons who have died of AIDS was also 100 per cent[3].

The evidence from the sharp injury and HIV contamination register from the Centre for Disease Control (CDC) in Atlanta, Georgia, USA, is similarly compelling (Reference 4 and personal communication, CDC, 1990). At this time the register is tracking the progress of 1931 known exposures of health care workers to proven HIV-positive blood. Only three seroconversions have occurred and all have been after deep intramuscular penetrations by needles whose bores probably contained the infected blood at the time. Two of these dramatic injuries occurred during major cardiac resuscitation and in the third the worker was impaled on an upturned dirty needle (personal communication, CDC, 1990). No seroconversion has occurred after 135 operating theatre injuries and none in 165 open wound or mucous membrane exposures. Only 7 per cent of all the episodes recorded were in the operating theatre area and only 15 per cent of the involved health care workers were physicians or surgeons – none of whom has seroconverted. The world-wide current total from our own Public Health Laboratory Service at Colindale is 9 documented seroconversions in 15 prospective trials involving 2475 exposures (0 36 per cent). None of these, however, was a surgeon, and four suspected transmissions to surgeons have all concerned work in sub-Saharan Africa (Heptonstall J, personal communication, 1990).

The surprising failure so far of 'the dog to bark' itself demands investigation which might provide clues for improvement in surgical safety precautions. The precise microanatomy of the needle injury probably merits closer scrutiny. The curious predominance of deep needle sticks by hypodermic needles containing blood suggests that positive pressure inoculation into a vascular space may be a key factor. The well established association in the wider world with anoreceptive and sometimes violent homosexual activity and intravenous drug abuse would accord with this hypothesis.

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Whatever the number of reported incidents all surgeons know that there must have been literally hundreds of thousands of suture-needle or scalpel injuries to surgeons and scrub nurses during the last ten years. Indeed the predominance of non-operating room exposures in the CDC series probably reflects reluctance of relatively 'hardened' surgeons to report 'sticks' whose true incidence may be much higher than those with hypodermic needles, so that even a 1 in 200 risk would be a substantial threat. Curious indeed, therefore, that the dog remains almost entirely silent! Presumably the absence of a lumen within a suture needle – the commonest cause of surgical 'needle stick' injury – means that blood particles, confined to its surface, tend to be held up at the portal of entry and not carried deep to the skin with the same facility as with a hollow bore needle. Could a film of antibacterial from the recent 'scrubbing' be a further factor in the apparent rarity of inoculation in the surgical setting; and could further protection be provided not only by 'double gloving' but by wearing the gloves 'wet' with an effective antiviral agent between the skin and the rubber? This 'third layer' of protection could readily become routine in the operating theatre if its value could be demonstrated.

What therefore should be done at this time? Research into the actual transmission of HIV, improvement in ward and theatre discipline with 'sharps', and improvement in hand protection for surgeons are all compellingly obvious. Clearly we must stop passing knives and sharp instruments to each other directly and surgeons must abandon the practice of using a finger of their left hand to guide suture needles through tissues. Clearly the 'surgical stick' has a different microanatomy from the 'hypodermic stick' and needs to be studied separately. Interestingly a British Company has devised a hypodermic needle which can pass through the skin only once and which is protected after withdrawal by an automatic sleeve which locks over the point. Perhaps such needles should become routine on cardiac arrest trolleys and in certain 'high risk' areas[5]. Is it however entirely sensible for surgeons to be plodding around like spacemen in thigh length boots and peering through goggles when the evidence suggests that the major risk is elsewhere in the hospital, involving a different kind of needle and a different group of health care workers? The cost of thus cladding the theatre team in the approved CDC manner was recently calculated, no doubt with a dash of cynicism, as $129 million per probable seroconversion prevented[6]! The implications of widespread testing for every patient or for health care workers are similarly out of proportion to the possible gain – which workers, how often, how to make use of the information while respecting the confidentiality of the individual, how to prevent scaremongering and punitive financial loading of workers who acquire by implication a 'high-risk' status which remains utterly unproven, what other tests such as those for hepatitis should be done as well, and what action should be taken about the greater number of hepatitis carriers that will be thus uncovered?

It would be foolish and irresponsible to fail to respond to the obvious threat of AIDS in the health care setting. As with other major challenges however it is essential that money should be sensibly spent and that scientific objectivity should not be subjugated to political or media 'hype'. One urgent priority, for example, is to develop a system of testing blood products so as to eliminate the 'window' period between infectivity and seropositivity.

The situation in the operating theatre however requires careful and objective evaluation. With the exception of homosexuals and drug abusers there is no evidence to regard any surgeon as being in a high risk group, and no evidence to justify the idea that even an infected surgeon is *per se* a danger to others. Worker to patient transmission is many times less probable than the reverse for many reasons; only the most psychopathic of health care workers would respond to a needle stick by plunging the needle into a patient, and significant volumes of surgeon's blood are seldom inoculated into patients. It seems eminently reasonable however that any patient from a high risk group being offered a 'high risk' procedure should be asked to undergo voluntary testing as an extra protection for all concerned in their care, particularly nurses, anaesthetists and the resuscitation team. Even modest initiatives to extend testing of this kind however encounter serious problems due to the four Cs – consequences, confidentiality, counselling and consent. Possibly some of these could be overcome by introducing a *virus profile* test for selected patients incorporating hepatitis A, B, C, Delta agent, and HIV 1 and 2, plus others as they emerge. There could be guaranteed confidentiality and anonymity regarding the HIV component, plus feedback and counselling for those who opt for it. All *virus risk* patients could then be handled similarly with extra care and the greater risk of hepatitis transmission would automatically be covered. It is a matter of considerable relief that there appears to be no sustainable case at this time for the widespread testing of nurses, surgeons or other hospital employees for HIV itself. If this should become truly necessary to protect the lives of patients then the wider issues will have to be faced. However the threatening nature of repetitive testing would blight the lives of those who work in our hospitals and cast a dark shadow over their working environment. The practice of surgery in particular would indeed never be the same again.

Let us hope that this particular dog continues to remain silent!

R. J. Heald

Colorectal Research Unit
Basingstoke District Hospital
Basingstoke
Hampshire
RG24 9NA
UK

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Announcement

We would like to inform all potential authors that the editorial office of The British Journal of Surgery is changing address. From 21 January 1991, please address all correspondence to. The British Journal of Surgery, Butterworth–Heinemann Limited, 59/60 Grosvenor Street, London W1X 9DA, UK. We will supply details of telephone, facsimile and telex numbers as soon as they are available.

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Infrarenal abdominal aortic disease: a review of the retroperitoneal approach

P. A. Grace and D. Bouchier-Hayes

Department of Surgery, The Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland

Correspondence to:
Professor D. Bouchier-Hayes

Transabdominal exposure is the most widely used surgical approach to the infrarenal aorta. Over the last 30 years a number of surgeons have championed the retroperitoneal approach for repair of abdominal aortic aneurysms and aortoiliac occlusive disease using a variety of incisions. Several studies attest to the clinical superiority of this approach over the transabdominal route and recent evidence demonstrates reduced physiological disturbance with this technique. The retroperitoneal approach is suitable for all elective operations on the abdominal aorta, particularly in patients with high-risk aneurysms and in selected patients with symptomatic and ruptured aneurysms.

The incidence of abdominal aortic aneurysms is continuing to rise[1,2] and, as the proportion of the population aged over 65 years increases[3], this condition will continue to be a major source of mortality and morbidity in the elderly[4,5] Screening programmes have been advocated to find and treat electively patients with asymptomatic aneurysms in the community[6], and advances in anaesthesia and vascular surgery have reduced the mortality for elective repair of abdominal aortic aneurysm to <5 per cent[7–9]. Transabdominal aortic endoaneurysmorrhaphy with graft replacement as evolved by Creech[10] is now the generally accepted and most widely applied surgical approach to infrarenal abdominal aortic aneurysms[7,8,11]. However, it has been recognized for many years that the aorta can be approached by the retroperitoneal route with significant improvement in operative morbidity and hospitalization[12,13]. The purpose of this analysis is to review the impact of the retroperitoneal approach to the infrarenal abdominal aorta on the management of patients with aneurysmal or occlusive aortic disease.

Historical development

John Abernathy first described the retroperitoneal approach when, in 1796, he tried unsuccessfully to ligate an external iliac artery aneurysm by this approach[14]. In 1834 Murray, in South Africa, reported a case of ligature of the abdominal aorta and commented that 'the operation was more tedious than difficult and at one time the patient needed some brandy and water to support him'. Unfortunately, the patient died 23 h after the operation[15]. Sir Astley Cooper used the retroperitoneal approach 2 years later to ligate the external iliac artery in a patient with a femoral aneurysm[16].

The first resection of an abdominal aortic aneurysm was performed in 1951 by Dubost, who gained access to the aorta extraperitoneally via a left thoracoabdominal incision[17]. Rob in 1963 reported 500 cases of aortic reconstruction in which he used the retroperitoneal route and observed a better postoperative course in these patients compared with patients undergoing transperitoneal aneurysm repair[12]. However, he cautioned against the retroperitoneal route in patients with large aneurysms or aneurysms which extended to the juxtarenal level. Although impressed with the decreased morbidity associated with the procedure, he commented that retraction was difficult. This may have been because of poor patient positioning and an inadequate incision[12]. Rob also noted that ruptured aneurysms could be satisfactorily excised via the retroperitoneal approach and that the extravasated blood had dissected the retroperitoneum in many cases.

In the succeeding 20 years the technique was championed by Stipa and Shaw[18], Helsby and Moossa[19] and Stoney and Wylie[20], who approached thoracoabdominal aneurysms via a transpleural chest incision extending across the costal margin into the true retroperitoneal space from the left side. More recently Taheri *et al.*[21], Williams *et al.*[22], Sharp and Donovan[13], Corson *et al.*[23] and Leather *et al.*[24] have all reported their experiences with the retroperitoneal approach and have all observed improved morbidity following this technique. Shepard *et al.*[25] advocated the retroperitoneal approach for high-risk abdominal aortic aneurysms in 1986, and in 1988 Chang *et al.* reported nine patients with ruptured aneurysms in whom aneurysm repair was achieved via the retroperitoneal route[26].

Operative technique

The patient is positioned in a semilateral position with the left side up. The shoulders are fixed at approximately 60° to the horizontal plane by means of a sandbag under the left shoulder, while the pelvis is allowed to rotate posteriorly so that it lies at an angle of approximately 45° to the horizontal plane. A suction beanbag device may be valuable in maintaining this position[26]. By rotating the table towards or away from the operating surgeon, more or less lateral position can be achieved. The use of the kidney bridge to break the table considerably increases the space between the costal margin and the iliac crest. This position gives excellent access to the retroperitoneum and to both groins if necessary.

A number of different incisions have been described for the retroperitoneal approach to the aorta including:

1. A midline extraperitoneal incision[27]
2. A left iliac fossa incision[12].
3. A cresentic left paramedian incision only[19,21] or with an oblique extension on to the left anterior chest wall[28].
4. A transverse left upper abdominal incision[29].
5. Various flank incisions[13,22,24–26,30,31]

The left iliac artery, aortic bifurcation and distal aorta can be approached retroperitoneally by vertically extending a longitudinal inguinal incision cephalad on to the abdominal wall to the level of the umbilicus – the Peter Martin approach[32,33]. The proponents of the paramedian incisions have observed less postoperative pain compared with flank incisions, presumably because there is less dissection of muscle

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posteriorly using this approach. Risberg's extension of the paramedian incision gives excellent access to the suprarenal aorta[28].

However, an oblique flank incision is currently favoured by most surgeons[13,22,24–26,30,31]. The incision extends in a curvilinear fashion from the lateral border of the rectus muscle anteriorly adjacent to the umbilicus to the eleventh interspace posteriorly. Using electrocautery, the incision is deepened posteriorly through the lower fibres of the latissimus dorsi and the underlying edge of the serratus posterior inferior and anteriorly through the external and internal oblique muscles. The lumbar fascia is incised posteriorly to expose the loose fat of the retroperitoneal space. By blunt dissection the peritoneum is separated from the posterior surface of the transversus abdominis, which is then divided.

The retroperitoneal space is initially developed inferiorly by blunt finger dissection separating the posterior peritoneum from the iliopsoas muscle taking care to stay anterior to the epimysium of the iliopsoas muscle. This manoeuvre exposes the inferior aorta just above the bifurcation and the left common and external iliac arteries. The dissection then proceeds cephalad, developing the plane between the iliopsoas muscle and the perirenal fascia with its enclosed fat. Most authors advocate mobilization and medial displacement of the left kidney and ureter, thus exposing the entire infrarenal aorta[24–26]. In infrarenal aneurysms, however, Sicard *et al.* prefer to leave the left kidney in its anatomical position and dissect the left ureter off the peritoneum and retract it laterally to prevent traction injury[30,31]. We have also used this approach on a number of occasions and found that it gives adequate exposure. The left renal artery is easily identified by a line dropped vertically from the tip of the 11th rib

After systemic heparinization, the iliac arteries should be controlled initially to minimize the potential for distal embolization[24] This can usually be achieved by lifting the artery forward with a Babcock forceps and applying a shod Fogarty clamp. If difficulty is encountered in placing an external clamp on the right iliac artery, control can be achieved later, after opening of the aneurysms sac, by using balloon intraluminal catheter occlusion. The neck of the aneurysm is approached from its posterolateral aspect. The large lumbar branch of the left renal vein is identified, ligated, suture ligated and divided. The plane posterior to the neck of the aneurysm is developed by blunt dissection close to the vertebral body. The anterior plane is similarly opened so that a straight shod Fogarty clamp can be applied. No attempt is made to dissect the aorta free circumferentially.

When supracoeliac control is necessary the dissection proceeds cephalad along the aorta towards the left crus of the diaphragm, which is divided in the long axis of the aorta[25]. When approaching a ruptured aneurysm by the retroperitoneal route a hand is inserted along the diaphragm until the crus and underlying supracoeliac aorta are encounterd. Manual pressure is applied to the aorta with the left hand while with the right hand the crus is divided transversely immediately caudal to the area of compession and an aortic clamp applied[26]. The retroperitoneal space is then opened as for an elective aneurysm, a clamp is placed at the neck of the aneurysm, and the supracoeliac clamp is removed[26].

Although most surgeons open the aneurysm sac longitudinally along its posterolateral wall and insert a tube or bifurcated graft using the Creech technique[25,30,31], Leather *et al.* prefer to exclude the aneurysm and perform an end-to-end anastomosis between the divided proximal and distal aorta and the graft. The aneurysm sac is oversewn to exclude it[24]. These authors have argued that this technique reduces blood loss by 40–45 per cent compared with opening the aneurysm sac[24].

After the aneurysm sac is opened, back bleeding from the lumbar and inferior mesenteric arteries is controlled by suture ligation, and the upper anastomosis is performed in the standard fashion. Whenever possible a tube graft should be inserted as this obviates the need to expose the femoral or external iliac arteries. However, in patients with iliac aneurysms or iliac occlusive disease, distal anastomoses are carried out to the iliac or femoral arteries as necessary. The right limb of a bifurcated graft can be easily passed in a retroureteric fashion into the right iliac or right femoral area[30,31]. Shepard *et al.* advocate anastomosing the distal limbs of a bifurcated graft to the external iliac arteries as it is easier and avoids the complications of a groin incision. This is achieved on the left side through the retroperitoneal incision and on the right side through a small right lower quadrant incision[25].

Indications for the retroperitoneal approach

The most frequent indication for the retroperitoneal approach is the elective repair of infrarenal abdominal aortic aneurysm[22–24]. It is especially useful in patients with high-risk aneurysms[25,31] Shepard *et al.* used the retroperitoneal approach in 23 patients who had either anatomically complex aneurysms ($n=19$) or were medically high-risk patients ($n=9$) or both ($n=14$). Three of their patients had undergone previous abortive attempts at aneurysm repair via the transperitoneal route. There was a single postoperative death (4 per cent) in this high-risk group of patients[25] Sicard *et al.* used the retroperitoneal route for aneurysm repair in 21 high-risk patients (American Society of Anesthesiologists anaesthesia risk classification IV) with a single death and an average postoperative hospital stay of 24 days. These patients, who had significant chronic pulmonary disease, recent (i.e. within 3 months) myocardial infarction, congestive cardiac failure or significant arrhythmias, would not have been considered for aneurysm repair by the transperitoneal route[31].

Ruptured abdominal aortic aneurysms have also been approached via the retroperitoneal route, and Rob in 1963 commented that ruptured aneurysms could be satisfactorily excised via this approach and that in many cases the extravasated blood will have stripped the peritoneum allowing for rapid clamping of the aorta[12]. Unfortunately, he did not give details of the patients who underwent this approach for ruptured aneurysms. Chang *et al.* using a renal type incision, reported the use of left retroperitoneal aortic exposure in ruptured ($n=9$) or symptomatic ($n=16$) abdominal aortic aneurysms[26]. Without exposing the aneurysm, a hand was inserted along the diaphragm until the crus and underlying supracoeliac aorta were encountered, and manual pressure was applied compressing the aorta against the vertebral column. Manual control could be gained reliably within 5 min of intubation. An addition 1–2 min was required to place a clamp on the supracoeliac aorta. They had four deaths (16 per cent), one in the rupture group (11 per cent) and three in the symptomatic group (19 per cent). All patients regained intestinal function within 2 days of operation and all appeared to do better than previous patients with transperitoneal emergency surgery in terms of intensive care and hospital stay[26]. The retroperitoneal route has also been used to gain access for juxtarenal and suprarenal aneurysms[31].

Aortoiliac occlusive disease is the other main indication for the retroperitoneal approach to the abdominal aorta and iliac arteries. It has been used extensively for aortoiliac disobliteration[19], aortoiliac bypass, aortofemoral bypass, iliopopliteal bypass, coeliac and renal artery angioplasty or bypass, and mesenteric occlusive disease[29,31,34]. Metz and Mathiesen reported their experience of the retroperitoneal approach for aortoiliac disease in 52 patients and observed decreased mortality and morbidity compared with the transperitoneal approach in 17 patients[29]. Johnson *et al* used the extraperitoneal route in the management of 298 patients with claudication ($n=189$) or critical limb ischaemia ($n=109$)[35] Of these patients, 106 underwent thromboendarterectomy and 192 had a graft inserted. The 30-day mortality rates for claudication and limb salvage were 1·6 and 8·3 per cent respectively, with significant improvement in morbidity (38 *versus* 49 per cent) compared with 161 comparable patients treated by the transperitoneal route However, the mortality rate was 4 per cent for both groups of patients[35].

Advantages and disadvantages of the retroperitoneal approach

The earliest proponents of the retroperitoneal approach observed that it led to a smoother, faster, less complicated postoperative course with a low incidence of pulmonary complications and ileus[12,18,19,21,27,29,34]. To date only one prospective randomized study comparing the retroperitoneal and transabdominal approaches to the abdominal aorta has been reported[36]. Cambria *et al.* randomized 113 patients undergoing elective abdominal aortic reconstruction to transabdominal ($n=59$) or anterolateral retroperitoneal approaches ($n=54$) They were unable to demonstrate statistically any important differences between the two approaches. However, there were slightly more patients with aneurysms than aortoiliac occlusive disease in the retroperitoneal group (74 *versus* 58 per cent) and they observed a trend towards reduced mortality, morbidity, postoperative ileus and hospital stay in the retroperitoneal group (*Table 1*).

A number of other authors have also compared the two approaches, but the patients in the transperitoneal groups were either historical controls[29] or concurrent but unrandomized controls[24,30,31,35]. However, combining all of these analyses gives a total of 1153 patients who underwent aortic surgery via the retroperitoneal ($n=712$) or transabdominal routes ($n=441$) (*Table 1*). The operative mortality rate was similar for both groups at 3 and 4 per cent for retroperitoneal and transperitoneal approaches respectively, but morbidity in the retroperitoneal group was only 28 per cent compared with 39 per cent for the transperitoneal group Hospital stay was also significantly reduced in the retroperitoneal group (10·8(2·9) *versus* 15·8(4·4) days, mean(s.d.)). Postoperative ileus occurred less often in the retroperitoneal group occurring in only 2 per cent of patients compared with a rate of 9 per cent for the transperitoneal route[24,29,35,36].

Sicard *et al.* comparing two groups which although not randomized were well matched, observed a significant decrease in postoperative nasogastric intubation (57 *versus* 98 h) and a shorter time to initiation of alimentation (3 *versus* 5 days) in the retroperitoneal group[30]. Similarly, Cambria *et al.* in their prospective randomized study observed earlier resumption of liquid (3·4(1·3) *versus* 4·0(1·4) days) and solid (5·1(1·7) *versus* 6·0(2·2) days) diets (mean(s.d.)) with the retroperitoneal approach[36]. Sicard *et al.* also observed that patients undergoing the retroperitoneal operation had reduced blood loss (mean(s.d.) 1296(109) *versus* 1950(196) ml), required less crystalloids and had better peroperative urinary outputs[30] Leather *et al.* also reported a reduced intraoperative blood loss with the retroperitoneal approach (1321 *versus* 1756 ml)[24]. Finally, Sicard *et al.* estimated the hospitalization costs of the two approaches and calculated that the retroperitoneal approach resulted in a mean saving of $2587.00 (mean(s.d.) $12 549(778) *versus* $15 136(905))[30,31].

There are a number of theoretical drawbacks to the retroperitoneal approach. Firstly, some time may be spent positioning the patient on the table, but with the Risberg incision we have not found this to be the case. A frequently quoted disadvantage is the inability to explore the abdomen for other pathology before aneurysm repair. Although associated significant conditions have been reported with abdominal aortic aneurysms, most of these are asymptomatic gallstones[37]. However, preoperative evaluation of patients with abdominal aortic aneurysms using faecal occult blood testing, sonography and computed tomographic scanning should detect most unsuspected pathology. Furthermore, the left side of the colon, where most colonic malignancies are to be found, is easily palpable through the peritoneum via the retroperitoneal route. Lastly, operating on the aorta via the retroperitoneal approach is technically demanding, access to the right renal artery is difficult and exposure of the right iliac system may require a right lower quadrant counterincision.

Physiology of the retroperitoneal approach

Although many authors have observed better results following the retroperitoneal approach for aortic reconstruction[24,29–31,35], few physiological data exist to explain this benefit. To determine whether the retroperitoneal approach offered any physiological advantage over the transabdominal approach, Hudson *et al*[38] compared cardiac dynamics and blood levels of 6-ketoprostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) during exposure of the aorta in 52 patients, 33 of whom underwent transabdominal and 19 retroperitoneal exposure of the aorta They found that mean arterial pressure and systemic vascular resistance decreased and cardiac index and heart rate increased and facial flushing occurred 10 min after bowel exploration in the transabdominal group. These haemodynamic alterations correlated in time and magnitude with a 14-fold increase in 6-keto-$PGF_{1\alpha}$. None of these changes was observed in patients undergoing retroperitoneal exploration, and these authors speculated that the absence of the response to bowel exploration may account for the observed advantages of the retroperitoneal approach. Whether indomethacin might inhibit the haemodynamic effects during the transabdominal approach to the aorta is currently under study[38].

In a prospective analysis of 20 patients, O'Sullivan and Bouchier-Hayes[39] compared lung volume and gas exchange changes during and after elective abdominal aortic aneurysm

Table 1 *Comparison of retroperitoneal and transperitoneal approaches to the abdominal aorta*

	Retroperitoneal approach					Transperitoneal approach				
Study	*n*	Mortality	Morbidity	Hospital stay (days)	Ileus	*n*	Mortality	Morbidity	Hospital stay (days)	Ileus
Metz and Mathiesen (1978)[29]	52	5(10)	27(52)	15	3(6)	17	2(12)	10(59)	23	6(35)
Johnson *et al.* (1986)[35]	298	12(4)	112(38)	12	3(1)	161	6(4)	79(49)	17	10(6)
Sicard *et al.* (1989)[31]	115	0(0)	–	10	–	98	3(3)	–	14	–
Leather (1989)[24]	193	7(4)	14(7)	7	1(0·5)	106	4(4)	23(22)	12	11(10)
Cambria *et al.* (1990)[36]	54	0(0)	16(30)	10	2(4)	59	1(2)	19(32)	13	4(7)
Total	712	24(3)	169(28)		9(2)	441	16(4)	131(38)		31(9)
Mean(s.d.)				11(3)					16(4)	

Values in parentheses are percentages except where otherwise stated resection using transabdominal ($n=9$) or retroperitoneal ($n=11$) routes. They found that intrapulmonary shunting and alveolar/peripheral arterial oxygen gradients were significantly lower in the retroperitoneal group during the cross-clamp period and 24 h after surgery. Functional residual capacity was significantly reduced in the transabdominal group for up to 8 days after operation. Thus, the retroperitoneal approach was associated with significantly better perioperative oxygenation and preservation of lung volumes. These authors speculated that preservation of diaphragmatic contractility may be better with the retroperitoneal route, and suggested that it may be the preferred approach for elective repair of abdominal aortic aneurysms[39].

Conclusions

Since the inauguration of the modern era of aortic surgery by DuBost *et al.*[17] in 1951 a number of surgeons have used the retroperitoneal approach to the infrarenal aorta. However, the majority of surgeons still cling to the transabdominal route. Although the only prospective randomized trial performed to compare the retroperitoneal and transabdominal approaches to the aorta found no important advantage for the retroperitoneal route[36], several retrospective studies attest to the superiority of the retroperitoneal approach. All of the reports document decreased morbidity and hospitalization following this approach[24,29–31,35,36]. The reduced postoperative morbidity associated with this approach is particularly valuable in the frail, the very old and those with cardiopulmonary disease. Of the various incisions used we have found that the lateral paramedian incision carried obliquely onto the chest wall (Risberg incision) gives the best exposure. We believe that the retroperitoneal route should be the standard approach for elective surgery of the infrarenal aorta, and in selected patients it should be considered in emergency procedures. 'It is not a difficult operation for the surgeon. It is without doubt a much easier operation for the patient'[35].

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Recurrence of Crohn's disease after resection

J. G. Williams,
W. D. Wong,
D. A. Rothenberger and
S. M. Goldberg

Division of Colon and Rectal Surgery, University of Minnesota, Box 450 Mayo Building, 420 Delaware Street SE, Minneapolis, Minnesota 55455, USA
Correspondence to:
Mr J. G Williams

Recurrent Crohn's disease develops in most patients after surgical resection if the patient is followed for sufficient time. This review examines various aspects of recurrent Crohn's disease. It is concluded that Crohn's disease is a diffuse condition of the gastrointestinal tract and that radical resection of Crohn's disease does not prevent recurrence. Assorted factors thought to be associated with recurrence are examined and the relevance of these factors to the surgeon treating Crohn's disease is discussed.

In the early descriptions of Crohn's disease, surgical resection of diseased bowel was thought to be curative[1,2]. However, it was soon appreciated that recurrence after surgery was common, especially if the patient was followed for many years[3–5]. The aetiology of recurrent Crohn's disease, like the aetiology of the disease itself, remains uncertain. It is important that surgeons are aware of any factors within their control which might influence the risk of recurrence after surgery so that appropriate therapy is provided. Similarly, a knowledge of how various disease parameters relate to the risk of recurrence is important when advising patients with Crohn's disease about the possible long-term outlook after surgery Much has been written on this subject and this review focuses on the factors thought to be associated with recurrence of Crohn's disease after resection.

Recurrence or recrudescence

The semantics of the term 'recurrence' deserve consideration. Recurrence implies that a problem or condition returns after a period of absence, whereas recrudescence implies that a problem breaks out again after a period of dormancy. Morphometric studies have demonstrated increased numbers of inflammatory cells in grossly normal gastric[6], duodenal[6], jejunal[7] and rectal[8] mucosa in patients with Crohn's disease. Similarly, micrograr ulomas have been demonstrated in apparently uninvolved rectal[9] and colonic[10] mucosa. Changes in mucosal cell enzyme activity have been demonstrated in uninvolved bowel in patients with Crohn's disease[8,11,12] These findings imply that subtle changes are present throughout the gastrointestinal tract of patients with Crohn's disease. Recurrence may therefore represent a change from microscopic, subclinical disease to macroscopic disease with clinical manifestations. In this case, perhaps recrudescence is a better descriptive term. However, for the purposes of this review, we shall use the traditional term of recurrence, realizing that the disease may be present throughout the bowel, although primarily in a subclinical form.

Defining recurrence

The two most important determinants of the rate of recurrence in a cohort of patients undergoing resection for Crohn's disease are the method of defining recurrence and the length of follow-up. Recurrence has been defined in various ways[13], each method having good and bad features (*Table 1*). The importance of the effect of method used to define recurrence on the reported rate is highlighted in *Tables 2–4*. Recurrence rates vary between the different series, but in general are lowest when the re-resection rate is used[13,17,18,23,26]. Highest recurrence rates are found when all symptoms are included, regardless of whether there was any objective evidence to support the diagnosis of recurrence[13].

The method used to calculate the recurrence rate is also important. Crude recurrence rates may be misleading, because the length of follow-up is ignored. Thus the rate of recurrence will appear low in a group of patients followed for only a few years. Actuarial analysis[36] is a more accurate method of calculating recurrence rates when length of follow-up varies. The cumulative recurrence rate is calculated for each year of follow-up, based on the number of patients at risk of recurrence during that year. Studies where both crude and cumulative recurrence rates have been calculated[17,20,21,37] demonstrate that crude recurrence rates tend to be an underestimation.

Site of involvement of recurrence

Although Crohn's disease can involve any part of the gastrointestinal tract, one of the unexplained features of this disease is the predilection of recurrence for specific sites. After small bowel resection or resection of the terminal ileum, recurrence invariably develops on the proximal side of the anastomosis, with occasional involvement of the distal side[5,16,38–40]. Even after second and third resections, the perianastomotic area is the most frequent site of recurrent disease[40] With ileocolic disease, recurrence tends to develop on both sides of the anastomosis[41]. Rutgeerts *et al.*[42], in a fascinating study, documented the natural history of recurrence at ileocolic anastomoses, using colonoscopy. The earliest appearance of recurrence was aphthous ulceration in the ileal mucosa, immediately proximal to the anastomosis These features were present in 72 per cent of patients examined within 1 year of resection. More advanced lesions, seen 1–3 years after surgery, included thickening of the mucosal folds with larger, coalescing ulcers, both linear and serpiginous in configuration. These changes progressed, with ulceration extending across the anastomosis to involve colonic mucosa and also the development of stenosis at the anastomosis This study suggests that macroscopic evidence of recurrence almost always develops within a year of resection, but takes much longer for the recurrence to become clinically apparent.

After colectomy and ileocolic or colocolic anastomosis, recurrence tends to develop in the ileum proximal to the anastomosis, as well as in the remaining colon and rectum[40,43–45]. After proctocolectomy, recurrence, when it occurs, invariably develops in the ileum proximal to the stoma, but usually does not involve the actual stomal segment of the ileum[40,46–48]. However, recurrence may also develop elsewhere in the proximal bowel or colon, away from the anastomosis[49–51].

Why recurrence preferentially develops in the ileum proximal to an anastomosis is uncertain. The size of the anastomosis does not appear to be important as recurrence rates are similar whether wide side-to-side enterotomies are constructed or whether conventional end-to-end or end-to-side enterotomies are performed (H. Sue Ling, J. G. Williams and L E. Hughes, unpublished data). A recent study which

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Table 1 *Advantages and disadvantages of various methods of defining recurrence after resection for Crohn's disease*

Method of defining recurrence	Positive features	Negative features
Symptomatic	Most patients included	Symptoms may arise from other causes
Symptomatic, supported by endoscopic biopsy or radiology	More specific than using symptoms alone	Radiological changes difficult to interpret endoscopic biopsy may miss important histological changes, or be non-specific or unobtainable
Reoperation rate	Easy to quantify	Patients require reoperation for other problems (e.g. adhesions)
Re-resection rate of histologically proven Crohn's disease	Easy to quantify	Not all patients with recurrent Crohn's disease require re-resection

Table 2 *Symptomatic recurrence rates after resection for Crohn's disease*

		Length of follow-up (years)		Cumulative recurrence rate (%)			
Study	*n*	Range	Mean	5 years	10 years	15 years	20 years
Lennard Jones and Stalder[13]	78	1–15	–	31	58	–	–
Kyle[14]	62	2–20	–	18	33	–	–
McDermot *et al*.[15]*	36	0–19	8·5	80	–	–	–

* Included patients who underwent bypass procedures

Table 3 *Total recurrence rates after resection for Crohn's disease, based on symptoms, supported by radiological or pathological changes*

		Length of follow-up (years)		Cumulative recurrence rate (%)			
Study	*n*	Range	Mean	5 years	10 years	15 years	20 years
Lennard Jones and Stalder[13]	78	1–15	–	23	51	–	–
deDombal *et al*.[16]	168	0·5–20	–	22	35	–	52
Greenstein *et al*.[17]*	100	–	8	59	80	93	–
Nygaard and Fausa[18]	83	2–10	4	52	84	–	–
Kirkegaard *et al*.[19]	20	5–14	9	24	45	–	–
Hellers[20]	618	1–20	10·5	30	50	60	–
Karesen *et al*.[21]*†	59	1–24	10	29	35	45	45
Luke *et al*.[22]	41	0·5–18	9·5	33	52	52	–
Trnka *et al*.[23]*	113	0–49	19·5	29	52	64	78
Wolfson *et al*.[24]	102	<18	–	48	60	67	–
Lindhagen *et al*.[25]	207	0·5–20	10	42	51	53	–
Heen *et al*.[26]‡	113	2–18	–	49	76	–	–
Speranza *et al*.[27]‡	90	1–22	9·5	53	69	85	–

* Included patients who underwent bypass procedures, † included both primary resections and re-resections, ‡ recurrence mainly defined as a radiological abnormality, independent of any symptoms

examined the microcirculation in Crohn's disease[52] demonstrated a sequence of vascular damage which preceded mucosal ulceration and was focal, occurring at the level of the muscularis propria. These findings suggest that the aetiology of Crohn's disease may involve multifocal gastrointestinal infarction. This theory might explain the propensity for recurrent disease to develop in the perianastomotic region, where the blood supply to the intestine may be diminished.

Factors influencing recurrence

Although the aetiology of recurrent Crohn's disease remains undetermined, many factors have been thought to be important as predictors of an increased risk of recurrence. Each of these factors will be looked at in detail.

Age

The influence of the age of the patient on recurrence of Crohn's disease after resection has been looked at in two ways: the age of the patient at onset of Crohn's disease and the patient's age at resection.

Age at onset of the disease. A few studies have suggested that young age of onset of Crohn's disease is associaed with a worse prognosis after resection[14,29]. High rates of recurrence after resection in children with Crohn's disease have been reported from Great Ormond Street[53], Toronto[54] and Leeds[55]. Greenstein *et al.*[17] demonstrated a trend towards increased recurrence in patients in whom the disease had become manifest before the age of 25. At 5 years, the cumulative recurrence rate was 50 per cent in patients who were 25 years or younger at

Table 4 *Total recurrence rates based on re-resection after surgery for Crohn's disease*

Study	n	Length of follow-up (years)		Cumulative recurrence rate (%)			
		Range	Mean	5 years	10 years	15 years	20 years
Lennard Jones and Stalder[13]	78	1–15	–	16	26	–	–
Greenstein *et al.*[17]*	100	–	8	43	65	87	–
Nygaard and Fausa[18]	83	2–10	4	30	50	–	–
Mekhjian *et al.*[28]	88	<17	–	23	58	76	–
Cooke *et al.*[29]	167	20–45	24·5	38	56	66	71
Higgens and Allan[30]	180	0·5–49	16	18	36	51	55
Lock *et al.*[31]	391	<25	11·5	19	33	42	48
Trnka *et al*[23]*	113	0–49	19·5	22	38	55	66
Frikker and Segall[32]	105	0·5–17	7·5	22	32	48	–
Heen *et al.*[26]	113	2–18	–	30	40	–	–
Whelan *et al.*[33]	432	>10	13	38	57	70	–
Chardavoyne *et al.*[34]	187	2–48	10·5	25	36	40	57
Valiulis and Currie[35]	126	–	–	27	45	–	–

* Included patients who underwent bypass procedures

onset of Crohn's disease, compared with only 24% in patients over 25. However, with longer follow-up the recurrence curves merged and after 13 years of follow-up the rates were 88 and 80 per cent respectively.

The evidence that age at onset of disease does not influence the risk of recurrence is much stronger. A number of actuarial studies have shown no correlation between age of onset and subsequent recurrence rates[20,30,56]. Furthermore, the Birmingham experience of terminal ileal and ileocolic Crohn's disease in 67 patients younger than 16 years at onset of disease showed no difference in recurrence rates when compared with patients with adult onset of disease[57]

Age at first resection. Series using crude recurrence rates have shown that young patients have a higher risk of recurrence than older patients[16,48,58]. However, length of follow-up was likely to have been shorter in the older age group, resulting in apparently lower recurrence rates. Hellers[20] was able to show an association between the patient's age at resection and recurrence using actuarial analysis of a large number of patients. The cumulative recurrence rates after 10-years follow-up were 55 per cent for patients aged 25 years or less at operation, which was significantly higher than in patients aged over 40 years (40 per cent). Similar findings were reported by Frikker and Segall[32], who suggested that recurrence is likely to occur earlier in young patients. However, an association between age at resection and subsequent recurrence has not been observed in other series using similar methods of analysis[13,18,25,27,31,34,40,59].

Gender

A few studies have suggested that the sex of the patient influences the risk of recurrence after surgery, with slightly increased recurrence rates reported for both men[55] and women[13,14]. However, the overwhelming majority of authors concluded that the sex of the patient does not influence the risk of developing recurrent disease[18,23,27,31,34,37,48,56,58,59].

Duration of Crohn's disease before resection

A number of authors have suggested that recurrence was more frequent in patients with a history of Crohn's disease of 2 years or less before resection[13,16,30,49,51,60] Sachar *et al.*[59] used a much longer disease interval to divide their patients into two groups and reported a significantly higher recurrence rate in patients who had Crohn's disease for < 10 years compared with patients with disease for > 10 years. Cumulative recurrence rates at 5 years were 65 and 23 per cent respectively. These findings support a theory that an aggressive form of the disease, leading quickly to a requirement for resection, results in a higher risk of developing postoperative recurrence than a more indolent form of the disease (see below).

However, the opposite effect has also been reported. Speranza *et al.*[27] demonstrated significantly higher recurrence rates (based on radiographic changes alone) in patients with a preoperative history of > 5 years, compared with patients with a shorter history. Van Patter *et al.*[5], from the Mayo Clinic, reported a crude recurrence rate of 57·4 per cent in patients with a history of <2 years before surgery, compared with 72·9 per cent in patients with a longer history, although the number of patients undergoing bypass in each group was not given. To confuse matters further, Chardavoyne *et al.*[34] reported highest recurrence rates in patients with a preoperative history of 3–10 years.

Other studies have failed to show a relationship between disease duration and recurrence[20,23,25,26,37,40,55,56,61]. In a large Swedish series[20], the crude recurrence rate for patients with a history of <3 years was 39·8 per cent, which was similar to rates of 37·7 per cent for patients with a history of 3–6 years and 38·2 per cent for those with a history of > 6 years.

How can these different findings be explained? Firstly, the duration of Crohn's disease before resection is often hard to define for an individual patient The time between making the diagnosis and resection is generally easy to measure; however, symptoms will usually have been present for a variable period before the diagnosis is made and this interval is often hard to appraise. Secondly, the length of the preoperative history is a continuous variable and most studies have divided the group of patients studied into two roughly equal halves, based on an arbitrary period which varies from study to study.

Site of involvement in the bowel

Farmer *et al.*[62] identified different patterns of Crohn's disease, based on three main sites of intestinal involvement. ileocolic, with involvement of the distal ileum and right colon, small intestine, with disease confined to the small bowel; and colonic, with disease confined to the colon. These three clinical patterns were associated with significant differences in the symptoms experienced, complications of the disease that developed, and requirement for surgery, which persisted after prolonged follow-up[63].

Many studies have looked at recurrence rates in relation to the three clinical patterns of disease In those studies where an association was demonstrated[16,17,20,31,32,37,48,60], most agree that the risk of recurrence is lowest for colonic disease and highest for ileocolic disease, with small intestinal disease having an intermediate prognosis. Lock *et al.*[31] reported a cumulative recurrence rate after resection of ileocolic disease of 44 per cent at 10 years, which was significantly higher than the rate for small intestinal disease (33 per cent). Frikker and Segall[32] reported cumulative recurrence rates of 13 and 38 per cent at 10 years for small bowel disease and ileocolic disease respectively. However, after 15-years follow-up the recurrence rate for small bowel disease had risen to 40 per cent but the recurrence rate for ileocolic disease had remained constant.

The difference in recurrence rates between colonic disease alone and ileal disease, with or without colonic involvement, is more striking. Vender *et al.*[60] reported a crude recurrence rate of 18 per cent in patients undergoing total colectomy for Crohn's colitis where there was no ileal involvement, compared with 48 per cent in patients with Crohn's colitis with ileal involvement. In the Cleveland Clinic series[31,50], the 10–year cumulative recurrence rate for colonic disease was 23 per cent compared with 44 and 33 per cent for ileocolic and small bowel disease respectively. Similar differences in cumulative recurrence rates have been reported by other groups[16,17,20,37]. Other authors have suggested that colonic disease is associated with a higher risk of recurrence than other sites of involvement[32,34]. However, many of the patients with colonic disease underwent segmental colectomy only, which is associated with higher recurrence rates than total colectomy (see below). Similarly, studies which have shown no relationship between site of involvement and recurrence[23,25,27,55,59] have either been based on crude recurrence rates or included few patients with isolated colonic disease.

Previous resection

A number of authors have considered whether patients who have developed one recurrence are at increased risk of developing a second recurrence after their second resection. Van Patter *et al*[5] were the first to suggest that this was the case, reporting crude recurrence rates of 62 per cent after the first resection and 81 per cent after a second resection. Lennard Jones and Stalder[13] calculated that the cumulative probability for a second recurrence at 5 years was 57 per cent. This was considerably higher than the rate for first recurrence (16 per cent at 5 years). However, there were only 14 patients at risk for a second recurrence, a third of whom had had their original resection performed at another centre. A similar problem with small numbers was encountered in the National Cooperative Crohn's Disease Study[28], where only 13 patients were at risk of a second recurrence.

Both deDombal *et al.*[16] and Greenstein *et al.*[17] thought that the recurrence rate was lower after second resection. This conclusion was based on crude recurrence rates; therefore patients at risk of a second recurrence would have had less time to develop a recurrence. This bias was confirmed in the latter study when actuarial methods were used and the opposite effect was observed.

Hellers[20], in the largest study to date, followed nearly 200 patients who had undergone previous resection Cumulative recurrence rates at 5 and 10 years were 45 and 65 per cent respectively. These were significantly higher than the recurrence rates after the initial resection, which were 30 and 50 per cent respectively.

Three large series, however, from Oslo[18], Boston[23] and Birmingham[29,30], which used cumulative recurrence rates, have shown no difference between first recurrence rates and subsequent recurrence rates.

Indication for surgery

One of the difficulties encountered when correlating the indication for surgery with the subsequent recurrence rate is in the interpretation of what factor precipitated surgery, especially as most studies are retrospective and often there is more than one indication for surgery Notwithstanding these problems, attempts have been made to see if the indication for surgery influences recurrence. Hellberg *et al.*[37] showed no difference in recurrence rates between patients undergoing urgent or elective operations. Ellis *et al.*[56] stated that the indication for primary surgery did not correlate with the subsequent recurrence rate, although the numbers of patients with each of the three main surgical indications (obstruction, fistula or failure of medical treatment) were small. Chronicity of Crohn's disease, with failure to respond to medical treatment, has been associated with increased risk of reoperation[64], although this observation was based on crude recurrence rates only.

Perforating complications of Crohn's disease (abscess or fistula) have been thought to be associated with increased risk of recurrence compared with non-perforating indications for surgery. Whelan *et al.*[33] noted that patients with fistulae, both perianal and intestinal, had a significantly higher recurrence rate than other patients undergoing resection. However, perforation with abscess formation was not associated with increased recurrence. Farmer *et al.*[65] showed that patients who required resection for internal fistulae had a significantly shorter interval to recurrence than patients with other indications for surgery. However, other authors have not found an association between fistulous Crohn's disease and recurrence[23,27].

deDombal *et al.*[16] were among the first to suggest that two patterns of recurrence exist, early and late, which may reflect two different types of Crohn's disease. One type results in a chronic, indolent course with late recurrences, while the other displays more aggressive disease, characterized by early recurrence after resection. Other authors have demonstrated a similar biphasic pattern of recurrence[28,34]

A study of 770 patients from the Mount Sinai Hospital[66] is one of the most interesting in this regard. Roughly half of the patients had perforating indications for surgery, which included internal fistulae arising from chronic perforation, internal abscesses from subacute perforation, and free perforation. The other half had non-perforating indications, which included intractability of the disease, obstruction, bleeding and toxic dilatation A second operation was required in 292 patients, of whom 128 originally presented with a perforating indication for surgery. The indication for the second resection was perforating disease in 93 of these patients, in contrast to only 47 of the 164 reoperated patients who had presented originally with a non-perforating indication This difference was highly significant. Furthermore, the interval between resection and reoperation was significantly shorter for perforating indications. This study supports the concept of two forms of Crohn's disease proposed by deDombal *et al.*[16] and others[28,34]. Patients with perforating Crohn's disease tended to re-present with the same pattern of disease and at a shorter interval than patients with non-perforating disease

However, a similar study from the Cleveland Clinic[67] does not support this tidy division of Crohn's disease into two forms Of the 486 followed, 194 required a second resection. There was no agreement between the indication for first, second or third resections Furthermore, the interval between first and second resection was similar for the different indications.

The reasons for the different findings of these two studies are not immediately obvious. The proportion of patients in each group of indications differed; nearly 50 per cent of patients had perforating indications in the Mount Sinai study, compared with only 28 per cent in the Cleveland Clinic study. Greenstein *et al.*[66] gave greater emphasis to perforating indications, assigning any patient with a perforation to this group, regardless of the simultaneous existence of a non-perforating indication which may have been a more important indication for resection.

Extent of resection performed

The extent of resection performed for Crohn's disease is influenced, to a certain extent, by the site of involvement in the gastrointestinal tract. For terminal ileal disease with minimal

Table 5 *Recurrence rates after resection of colonic Crohn's disease*

Study	Length of follow-up (years)		Recurrence rate after proctocolectomy (%)			Recurrence rate after colectomy and ileorectal anastomosis (%)			Recurrence rate after segmental colectomy (%)		
	Range	Mean	*n*	5 years	10 years	*n*	5 years	10 years	*n*	5 years	10 years
New Haven[60]	–	8·5	34	27	40	–	–	–	–	–	–
Cleveland[48]	–	11·5	127	13	28	–	–	–	–	–	–
St. Mark's[69]	1–28	9·5	107	5	10	40	38	56	–	–	–
Leeds[72]	7–25	15	162	10	15	45	52	60	–	–	–
Birmingham[73]	–	–	74	19	24	63	28	43	–	–	–
Birmingham[74]	0–37	15·5	–	–	–	63	33	53	36	48	65

colonic involvement, the diseased segment is usually excised together with the caecum. The length of the proximal resection margin of macroscopically normal bowel varies from series to series[68]. For colonic disease, the surgical options are more diverse, so that segmental colectomy, subtotal colectomy and ileostomy or ileorectal anastomosis and proctocolectomy are all possible options[69].

The recurrence rate after resection of colonic Crohn's disease has been shown to be related to the type of surgery performed[70,71]. Recurrence rates are much lower after proctocolectomy than after any lesser procedure (*Table 5*). The influence of involvement of the terminal ileum on subsequent recurrence after colectomy is controversial. Some authors have shown no association[47,75,76], although Vender *et al.*[60] found a crude recurrence rate of 48 per cent in patients with terminal ileal involvement, compared with 18 per cent in patients whose disease was confined to their colon. However, the patients with ileal involvement had been followed longer In the Cleveland Clinic series[48], the cumulative recurrence rate at 11 years in patients without terminal ileal involvement was 23 per cent, compared with 46 per cent for patients with ileal disease.

A second factor that governs the extent of resection is the length of bowel involved. A number of studies have looked at the relationship between length of involved bowel and recurrence. Van Patter *et al.*[5] found no relationship between length of bowel involved and recurrence, when < 50 cm of bowel were involved, but thought that lengths of bowel > 50 cm were associated with an increased risk of recurrence. Other studies have suggested that recurrence is more common after resection of long lengths of diseased bowel[49,55,58,77]. However, Trnka *et al.*[23] showed no difference in the length of diseased ileum resected from 13 patients who did not develop recurrence and 23 patients who did develop recurrence.

A third factor that determines the extent of resection is the size of the resection margin of macroscopically normal bowel. This has generated considerable controversy over the years between conservative surgeons and radical surgeons. Atwell *et al.*[55] tried to identify, from the operative report, patients who had 'generous' resection margins and those who had 'skimped' resection margins. Recurrence occurred in 21 of 65 cases deemed to have adequate margins compared with 53 of 62 with possibly inadequate margins. However, the reliability of this retrospective analysis of resection margins can be questioned. Furthermore, in 30 patients it was not possible to assess the length of the resection margins from the operative report. Two Scandinavian series have reported lower recurrence rates after radical resection. Bergman and Krause[78] followed 84 patients who underwent radical resection of all diseased bowel with a resection margin of at least 10 cm of macroscopically normal bowel and 57 patients who had non-radical resections, where inflammatory changes were present in the remaining gut or the resection margin was < 10 cm. Crude recurrence rates after a mean follow-up of 10 years was 29 per cent in the former group, compared with 84 per cent in the latter. This difference in recurrence rates persisted when the patients were reviewed 8 years later and the minimum follow-up was 14 years (mean 18 years)[79]. It can be argued that only patients who had resection of all overt disease, with or without radical resection margins, should have been included. Including patients with residual disease would have exaggerated the recurrence rate in the non-radical group. In a similar study, Nygaard and Fausa[18] demonstrated a significantly lower recurrence rate during the first year after radical resection than after non-radical resection, although the number of non-radical resections performed was small. When the study was extended and expanded[26], actuarial analysis was performed and a similar finding was observed. At 2 years, the cumulative recurrence rate after radical resection was 28 per cent, compared with 52 per cent after non-radical resection. It should be pointed out, however, that the diagnosis of recurrence was based on radiological changes alone and that symptoms were not taken into account It is possible that a higher proportion of asymptomatic, radiological recurrences were present in the non-radical resection group.

Other studies have failed to find any association between length of resection margin and recurrence[23,27,77]. In an interesting study, Hamilton *et al.*[77] showed that patients who developed recurrent disease had shorter resection margins than those who did not. However, the length of the resection margin was inversely related to the length of active Crohn's disease resected; that is, patients with long disease segments tended to have short resection margins When the influence of margin length was analysed, independently of the length of active disease in the specimen, there was no relationship to recurrence. Thus reports claiming a poorer prognosis for short resection margins may reflect a longer length of active disease in these patients

Involvement of disease at the resection margin

The influence of disease at the resection margin on recurrence rates has been one of the more contentious areas in the surgery of Crohn's disease. A higher recurrence rate has been demonstrated after ileorectal anastomosis to diseased rectum than after ileorectal anastomosis to macroscopically normal rectum[44,80], although anastomotic complications were similar. Lower recurrence rates have been claimed for radical resections with macroscopically normal margins, compared with non-radical resections where the margins were involved[24,26,78,79]. However, the latter group often contained patients with residual disease after resection.

Microscopic changes at the resection margin have also been thought to influence recurrence. Some surgeons have emphasized the use of frozen section examination of the resection margins during surgery to identify normal bowel with which to perform the anastomosis[21,81,82] However, microscopic changes are easily missed in frozen sections[83,84].

Karesen *et al.*[21] reported a crude recurrence rate of 66 per cent in 12 patients who had microscopic evidence of disease at the resection margin compared with 14 per cent in 42 patients who were thought to have normal resection margins by the pathologist. The criteria used to define microscopic disease were not given, however. Lindhagen *et al.*[25] divided 110 patients into three groups, based on the histological appearance of the resection margin. Forty-one patients had normal resection margins, 39 patients had minor inflammatory lesions and 30 patients had major inflammatory changes such as ulceration, crypt abscesses and granulomas. The cumulative recurrence rate at 10 years for those patients with major changes was 73 per cent, a rate which was significantly higher than the rate for patients with normal (37 per cent) or minimally inflamed (44 per cent) resection margins.

Further evidence for the importance of microscopic disease at the resection margin was reported by Wolff *et al.*[85] from the Mayo Clinic. They identified 39 patients who had undergone resection of Crohn's disease, where one or other resection margin had microscopic evidence of Crohn's disease. This they defined as mucosal inflammation or ulceration, specifically excluding non-specific submucosal or intramuscular inflammation. The cumulative recurrence rate for this group was 90 per cent at 8 years, compared with a recurrence rate of 47 per cent for other patients undergoing resection for Crohn's disease. Three criticisms can be made of this study. Firstly, it is likely that the two groups were not similar Secondly, in the patients with disease at the resection margin, half had skip areas of active disease in the remaining bowel, which is known to be associated with a high recurrence rate[86]. Thirdly, patients with microscopic disease were identified from the original pathology report. The histological sections of all operated patients were not reviewed, specifically looking for evidence of disease at the resection margins.

Other authors have not found any association between microscopic changes at the resection margin and recurrence[27,34,87–91]. Pennington *et al.*[88] studied 97 patients undergoing 103 resections. Fifty-two specimens had normal resection margins, but microscopic changes were present in the other 51 specimens. There was no difference in crude or cumulative recurrence rates between these two groups of patients based on clinical recurrence, suture line recurrence or reoperation rates. Similar results were reported by Heuman *et al.*[89] and Cooper and Williams[90]. However, in both of these studies, minor histological changes were included as evidence of disease at the resection margin and the number of patients fitting the histological criteria of ulceration or granulomatous inflammation used by Wolff *et al.*[85] were small.

This controversy may now have finally been resolved by the introduction of a new approach to segmental strictures. In 1982, Lee and Papaioannou[92] described their initial experience with strictureplasty for relieving small bowel obstruction resulting from short intestinal strictures. In this operation, the strictured bowel was opened longitudinally through the stricture and then repaired transversely. There were no major complications, despite the inclusion of actively inflamed bowel in the suture line. Other groups, most notably that of Alexander Williams from Birmingham, have reported an increasing experience with this technique[93–96]. Even though anastomosis is performed through diseased bowel, recurrence tends to develop at other sites[93]. Actuarial analysis has shown no difference in site-specific recurrence (based on the need for further surgery at that site) between patients undergoing strictureplasty and patients undergoing conventional resection[97]. However, this may be because tight strictures represent burnt-out fibrotic disease, and one study has suggested that strictureplasty in areas of active disease has a high recurrence rate[95].

Thus it would appear from these studies that diseased resection margins are of little consequence for increasing the risk of recurrence. However, experience with strictureplasty is limited and the results of long-term follow-up are awaited with interest.

Presence of granulomas

Crohn's disease is characterized by the presence of non-caseating granulomas. However, the presence of granulomas is not a *sine qua non* for the diagnosis of Crohn's disease, as granulomas are absent in 30–40 per cent of cases[98]. The significance of granulomas in Crohn's disease remains uncertain. They are assumed to represent a response to an as yet unidentified aetiological agent, although another theory which has been proposed is that granulomas reflect a defect in macrophage function[99].

A number of studies have addressed the question of whether the presence or absence of granulomas in the resected specimen is a predictor of recurrence. Glass and Baker[100] reported that recurrence was significantly lower in patients where granulomas were identified in the bowel wall or lymph nodes compared with patients in whom no granulomas were identified. Chambers and Morson[101] also reported a poorer prognosis in patients with few granulomas in the resected specimen. However, the difference in prognosis was confined to patients with colonic or anal disease. It is interesting to note that over 80 per cent of patients studied by Glass and Baker had colonic disease. Trnka *et al.*[23] found no difference in recurrence in patients with ileitis, with or without granulomas, but noted a higher tendency to recurrence in patients with ileocolitis with granulomas, although this was not significant Other studies have shown no difference in crude or cumulative recurrence rates between patients who had granulomas in the resected specimen and those who did not[5,24,34,56,102,103].

A major problem in correlating prognosis with the presence or absence of granulomas is that the number of granulomas found in a specimen of Crohn's disease and the proportion of patients with granulomas is related to the diligence of the search for granulomas[102,104]. Wolfson *et al* [24] studied at least ten slides per specimen and found granulomas in 14 patients who were thought not to have granulomas in the original pathological report. It is possible, therefore, that in the earlier studies fewer patients would have been classified as not having granulomas with more thorough histological examination.

Immunological factors

A wide variety of immunological abnormalities has been demonstrated in patients with Crohn's disease[105,106] A significant decrease in circulating T cell and total lymphocyte counts has been reported in patients with long-standing disease[107,108], which is thought to reflect accumulation of T cells in the diseased bowel[109]. However, it has also been suggested that these changes reflect malnutrition[110], well nourished patients having lymphocyte counts similar to those of controls

Severe preoperative lymphopenia has been suggested as a predictor of recurrence after resection in Crohn's disease. Heimann *et al.*[111,112] reported a recurrence rate at 3 years of 67 per cent in patients with severe lymphopenia (lymphocyte count.1000 per mm^3), which was significantly higher than the rate (36 per cent) for the other patients. The patients were only followed for a short period and it would be interesting to know if the recurrence curves merged with longer follow-up, as other studies with longer follow-up have not shown any relationship between lymphopenia and recurrence[113]. In a similar study, tissue immunoglobulin G levels were shown to be greater at the resection margin and in the diseased segment of bowel in patients who developed recurrence, compared with patients who remained recurrence free, during short-term follow-up[114].

These immunological variables are probably markers of a more severe form of the disease, where risk of early recurrence is greater. Their relevance to long-term outlook, however, is uncertain.

Perioperative blood transfusion

Blood transfusion has been shown to have an immunosuppressive effect on the recipient[115,116], which is thought to account for the improved survival of transplanted kidneys[117] and to be associated with decreased survival after resection of colonic tumours[118]. Immunological mechanisms have been implicated in the aetiology of Crohn's disease[105,106] and a few studies have investigated the effect of blood transfusion on recurrence after surgery

Williams and Hughes[119] reported a recurrence rate at 5 years of 19 per cent in 28 patients with small bowel Crohn's disease who had received a blood transfusion in the perioperative period, which was significantly lower than the recurrence rate in 32 patients with small bowel disease who did not receive a transfusion (59 per cent). Similar findings were reported by Peters *et al.*[113], although a third study did not find such an association[120]. Further investigation in this area is required before firm conclusions can be made on the influence of blood transfusion on recurrence in Crohn's disease.

Drug treatment after resection

With the recognition that recurrence develops in a high proportion of patients after resection of Crohn's disease, attempts have been made to prevent recurrence by using drugs which have been shown to be effective, or were thought to be effective, in treating active disease. Trials evaluating steriods[86,121,122], sulphasalazine[121–124] and azathioprine[122] as prophylaxis against recurrence have been performed. In each case, drug treatment was no better than placebo in preventing recurrence.

These studies highlight some of the difficulties encountered by therapeutic trials in Crohn's disease In all the trials, the number of patients recruited was small. The Cardiff study[86] included only 26 patients who had no obvious residual disease after resection and even the multicentre National Cooperative Crohn's Disease Study[122] incorporated only 48 patients who had undergone resection of all macroscopic disease. Two Scandinavian trials have included more patients. Bergman and Krause[121] followed a total of 84 patients, demonstrating similar recurrence rates between patients treated with steroids and sulphasalazine for 33 weeks and patients given placebo Wenckert *et al.*[124] followed 66 patients given either sulphasalazine or placebo for 18 months after surgery, with similar recurrence rates in the two arms. Furthermore, they calculated that between 110 and 130 patients would be required in each group to obtain a high probability of showing a significant halving in recurrence rates in the drug treated group.

In all the trials reported, follow-up was short (2–3 years[86,121–123]). Recurrent disease can develop many years after resection and it could be argued that any trial of drug prophylaxis should extend over many years. However, potential side-effects of drug treatment, especially long-term steroids or immunosuppressants, would limit their use. In the National Cooperative Crohn's Disease Study[122], patients in the placebo group fared better than those in the active group, which the authors attributed to drug side-effects suffered by the treated group.

Discussion

This review has examined many factors that have been thought to influence recurrence after resection of Crohn's disease. Little attention has been paid to bypass operations, as these procedures are rarely performed now because of the high risk of recrudescence after bypass[125] and the potential risk of cancer developing in the excluded segment of bowel[126].

Crohn's disease is a diffuse condition of the gastrointestinal tract, with subtle changes present in macroscopically uninvolved bowel Thus surgical resection is unlikely to be curative and recurrence of macroscopic disease is almost inevitable after resection if the patient is followed long enough.

Two questions therefore arise.

Can the surgeon influence the risk of recurrence?

The surgical treatment of Crohn's disease can vary in a number of ways. Firstly, the surgeon has some influence on the interval between diagnosis and resection, with some surgeons advocating early surgery to limit complications of the disease However, it is uncertain whether the interval between diagnosis and surgery is related to the subsequent risk of recurrence, all other factors being equal Although some studies[13,16,30,43,59] have shown an association between short preoperative history and early recurrence, this is not a universal finding[20,23,25–27,37,40,48,55,56,61]. Therefore, it would seem unreasonable to defer surgery in a symptomatic patient with a short history, merely because of the potential risk of early recurrence.

The second factor which the surgeon can influence is the type of operation and extent of resection performed. The type of operation performed is of more relevance for colonic disease, where the surgical options are more varied than for small bowel disease. It is now well established that proctocolectomy is associated with lower recurrence rates than other lesser colonic resections (*Table 5*). However, this lower risk of recurrence is at the cost of an abdominal stoma, which many patients find unacceptable. Segmental colectomy and colectomy with ileorectal anastomosis, although associated with higher recurrence rates, have a place in the treatment of patients with colonic Crohn's disease, especially in young patients where the potential morbidity of pelvic dissection, a perineal wound and an abdominal stoma are avoided[74,75,127,128].

The length of 'normal' bowel that should be included as resection margins has been a contentious issue for some time, with a swing towards less extensive resection in latter years. The main protagonists of radical resection have been the Scandinavians, who have shown that the lower recurrence rates reported for radical resection were maintained with longer follow-up. However, in these studies, macroscopic disease remained in some of the patients with non-radical resection and this has been shown to be associated with a high recurrence rate[86]. Other studies have shown no difference in recurrence rates between patients with wide and narrow resection margins[26,27,77]. Therefore, it would seem prudent to resect the diseased segment of bowel with a sufficient margin so that the subsequent anastomosis is performed between supple bowel ends, mainly for ease of construction Extensive resection of normal bowel to try to prevent recurrence is unwarranted and puts the patient at greater risk of short bowel syndrome if further resections are required. A method of identifying strictures in the small bowel which are not obvious from external examination of the bowel has been described[56]. A balloon catheter, distended to 25 mm in diameter, is passed up and down the bowel through a small enterotomy. Narrowed areas are identified and dealt with by strictureplasty, limited resection or dilatation[94]. We have found intraoperative colonoscopy useful in identifying strictures from within the bowel lumen. This approach might be expected to result in a reduction in early recurrence by identifying and treating subclinical lesions at the time of surgery

The third factor the surgeon may consider is whether to perform frozen section studies of the resection margin to obtain a disease-free segment for anastomosis The current evidence indicates that this is a waste of effort. Microscopic changes of Crohn's disease are seen in areas remote from the macroscopically diseased area, reflecting the panenteric nature of this condition[6–10] Therefore, a very extensive resection may be required to obtain microscopically normal bowel at the resection margins. Furthermore, most studies which have looked at the results of anastomoses performed in areas of microscopic disease[27,34,87–91], together with the encouraging early results of strictureplasty through diseased bowel[93,97], show that there is probably no greater risk of recurrence in these circumstances. A further reason that frozen section examination is unhelpful is that it is more difficult to identify microscopic changes of Crohn's disease in cryostat sections than in paraffin sections[83].

A fourth factor which may be considered is whether the patient should receive any drug treatment after resection, in an attempt to prevent recurrence developing. This is an attractive idea, although the evidence to date has shown no benefit for prophylactic treatment with steroids, sulphasalazine or azathioprine[86,121–124]

Are there any factors that identify patients at increased risk of recurrence?

Many possible factors have been examined, with few having been shown consistently to be reliable prognostic indicators. Young patients have been thought to be at increased risk of recurrence. This notion is based, in the main, on studies reporting crude recurrence rates. Actuarial studies, in general, have not shown an association between age and recurrence. However, it should be remembered that an 18-year-old patient undergoing resection has a much greater probability of developing recurrence in their lifetime than a 60-year-old, merely as a result of the longer time the patient will be at risk. It also appears likely that a patient who has had a previous resection is at no greater risk of developing a second recurrence than of developing a first recurrence.

Whether the length of history before resection of Crohn's disease is a prognostic indicator remains unresolved. Many studies have failed to show any relationship between this variable and recurrence rates, although others suggest that a short history is associated with an increased risk of recurrence. This has led to a theory that an aggressive form of the disease, with a short history before surgery, is followed by early recurrence. Greenstein *et al.*[66] thought that perforating Crohn's disease may represent an aggressive form of the disease, which they showed was associated with increased recurrence. Others have failed to confirm this observation[67].

The site of intestinal involvement does appear to be a predictor of increased risk of recurrence. Most authors agree that patients with colonic Crohn's disease have a lower risk of recurrence than patients with small bowel or ileocolic involvement, and that small bowel disease has a better prognosis than ileocolic disease. The length of bowel involvement also appears to be related to outcome, with longer lengths of diseased bowel being associated with higher recurrence rates.

Pathological variables may also be predictors of recurrence. The presence of granulomas in the specimen is probably of little relevance to the risk of recurrence. However, other variables such as circulating lymphocyte counts, reflecting immunological abnormalities, may identify patients at increased risk of recurrence.

Conclusions

Most patients will develop overt recurrence after resection of Crohn's disease if they are followed for a long time. Subclinical changes, suggestive of recurrence, develop soon after surgery. Radical resection does not appear to protect against recurrence, therefore conservative resections should be performed to preserve intestinal length. What predisposes certain intestinal sites to the development of recurrent disease remains unexplained. Finding the answer to this conundrum will probably result in a better understanding of the aetiology of recurrence and may result in specific treatment aimed at preventing it.

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Proximal gastric vagotomy: follow-up at 10–20 years

G. W. Johnston,
E. F. A. Spencer,
A. J. Wilkinson and
T. L. Kennedy

Royal Victoria Hospital, Belfast
BT12 6BA, UK
Correspondence to:
Mr G. W. Johnston

From August 1969 to December 1989, 600 patients had elective proximal gastric vagotomy for duodenal ulceration with an operative mortality of 0·2 per cent. Of these, 372 patients had surgery over 10 years ago. Three hundred and forty-two patients survived for more than 10 years and, in a prospective study, 305 were reviewed, forming the basis of this 10–20-year follow-up report. Forty-six (15 per cent) have had recurrent ulceration; 80 per cent of these developed symptoms within 5 years and no patient has had recurrence after 13 years. Although 29 patients required reoperation for recurrent ulceration, the current patient satisfaction rate for Visick grades I and II is 92 per cent. Only two patients required reoperation because of gastric stasis. It is concluded that proximal gastric vagotomy is a safe and satisfactory first choice operation for duodenal ulceration.

As far back as 1957, Griffith and Harkins demonstrated that, in dogs, emptying remained satisfactory when the parietal cell mass was denervated if the antropyloroduodenal innervation was preserved[1]. They suggested that clinical application for duodenal ulceration appeared feasible. However, it was not until 1969 that parietal cell vagotomy without drainage was reported from Leeds and Copenhagen[2,3]. The elimination of the drainage procedure fulfilled its early promise of reduced problems from bile vomiting, dumping and diarrhoea. However, the initial euphoria for parietal cell vagotomy has been diminished by reports of high recurrence rates which increase with length of follow-up[4,5]. Indeed, one of the pioneer groups experienced such a high recurrence rate that they no longer recommend parietal cell vagotomy as a 'standard operative treatment for duodenal ulceration'[6]. We started performing this procedure in August 1969 and have since performed 600 elective proximal gastric vagotomies without drainage. This paper discusses the long-term results in those patients followed for more than 10 years

Patients and methods

Between August 1969 and December 1989, 600 elective proximal gastric vagotomies were performed without drainage for duodenal ulceration. Three hundred and seventy-two of these patients received surgery over 10 years ago, and form the basis of this 10–20-year review. There was one operative death from cerebral haemorrhage, giving a 0·2 per cent operative mortality. Forty-three patients have since died from unrelated causes with 29 of these deaths occurring within 10 years of their operation. Of the remaining 342 patients, it was possible to contact and review 305 (89 per cent) Thirty-seven patients have been lost to follow-up because of emigration, change of address locally or lack of interest so long after the operation. Of the 305 patients reviewed 226 were men and 79 were women. The average duration of symptoms before vagotomy was 12 (range 1–42) years and the average age at operation was 42 (range 12–73) years. Two hundred and eighteen operations were performed by two consultants and the remaining 87 by 13 senior registrars or registrars, usually under supervision. Standard proximal gastric vagotomy was carried out with particular attention to adequate distal denervation in the region of the antrum, thorough oesophageal clearance of residual vagal strands and cutting the peritoneum at the oesophagogastric angle to ensure division of the 'criminal nerve' of Grassi. During the period covered by the study, the gastroepiploic vessels and nerves opposite the incisura were not divided. Seventy-nine patients had additional procedures carried out at the time of the primary operation; some had more than one procedure. Twenty-three had cholecystectomy, 29 had fundoplication, and 31 had duodenoplasty for duodenal stenosis, care being taken to preserve the pyloric ring[7]. One patient required splenectomy because of accidental damage. Preoperative pentagastrin tests and 10-day postoperative insulin tests were performed on about 60 per cent of the patients Elderly patients and those with a history of coronary artery disease were not referred for acid studies and in some instances tests were abandoned for technical reasons. Routine review was carried out at a special gastric clinic by one physician who consulted the surgeon involved where appropriate. Patients were questioned regarding pain, flatulence, postprandial fullness, vomiting, dumping, diarrhoea and their satisfaction with the operative procedure. A standard questionnaire was completed for each patient at each visit. Postal or phone review was used only for those patients who failed to attend for review; these were usually elderly or well patients who did not wish to take time off work. Postvagotomy endoscopy was carried out only in symptomatic patients. Each patient was awarded a modified Visick clinical grading: Visick I, no symptoms, Visick II, easily controllable symptoms; Visick III, more severe symptoms with some disability; Visick IV, recurrent ulcer, reoperation or disabling symptoms. Information was transferred from the standard questionnaire to an Apple (Apple Computer, Inc., Cupertino, California, USA) microcomputer and analysed using Data Base 4 Plus (Stoneware Inc, San Raphael, California, USA). The recurrence rate was estimated using life table methods

Results

Mortality

There was one operative death from cerebral haemorrhage following the primary operation of proximal gastric vagotomy. No patient died following revision surgery.

Morbidity

No patient sustained oesophageal damage at the primary operation but one patient did require splenectomy as a result of operative trauma. In the group of 29 patients who had combined fundoplication and proximal gastric vagotomy, two developed lesser curve necrosis which required re-exploration, both patients survived without further problems. Two patients developed emptying problems after operation and required drainage procedures at 3 months and 6 months, respectively.

Of 305 patients followed up for more than 10 years, 46 (15 per cent) have had recurrent ulceration: 38 duodenal, five gastric and three prepyloric. There were 33 recurrent ulcers in 226 men (15 per cent) and 13 in 79 women (16 per cent). Forty-three patients with recurrent symptoms were diagnosed endoscopically but three presented as emergencies (two with haematemesis and one with perforation). Recurrences have been diagnosed between 6 months and 13 years after operation (*Figure 1*). Eighty per cent developed symptoms and 47 per cent were firmly diagnosed within 5 years. Although 127 patients

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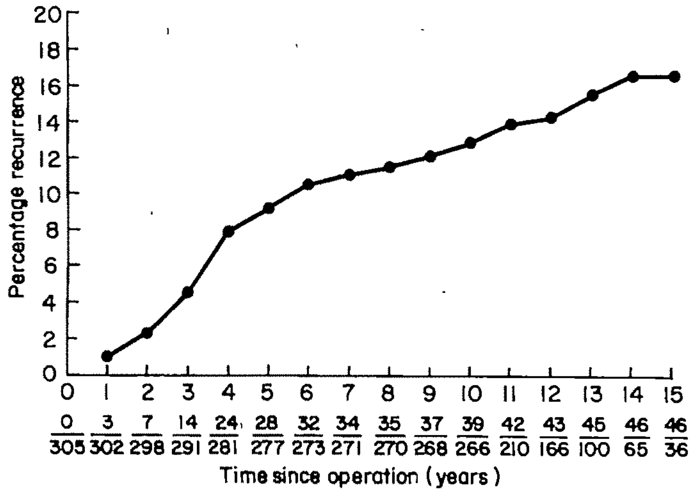

Figure 1 *Recurrent ulceration in the 305 patients followed for 10 to 15 years. The figures below the graph are the number of patients with recurrent ulceration over those eligible for analysis by life table methods*

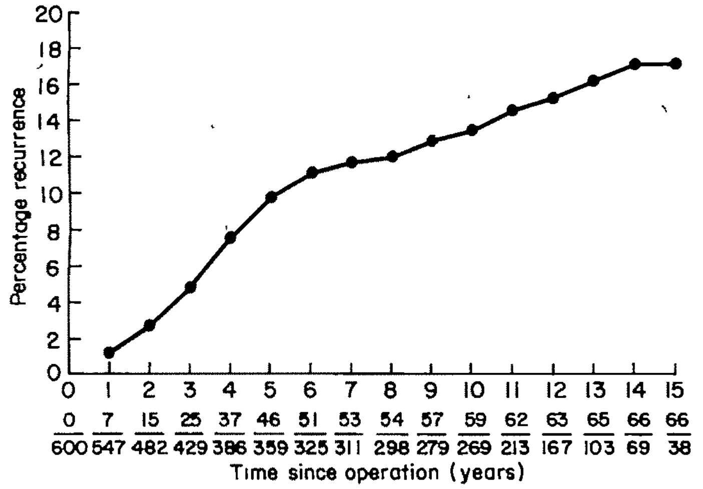

Figure 2 *Recurrent ulceration in a total series of 600 patients. The figures below the graph are the number of patients with recurrent ulceration over those eligible for analysis by life table methods*

have been followed for more than 13 years, no patient has developed recurrent ulceration after this time.

In the total series of 600 patients undergoing surgery in the 20-year period, there have been 66 recurrent ulcers (*Figure 2*). This includes five recurrences in the group of 67 patients who were operated on more than 10 years ago but who have either died or were lost before the 10–20-year period now under review.

Reoperations for ulcer

Today the majority of recurrent ulcers can be managed by treatment with histamine (H_2) receptor antagonists. However, earlier in the series most recurrent ulcers underwent revisional surgery. Twenty-two patients were treated by revagotomy and antrectomy, two by gastrectomy and two by gastrojejunostomy. Following this, only one patient developed a further recurrent ulcer. In this case the Zollinger–Ellison syndrome was responsible and the patient was treated by distal pancreatectomy and is currently Visick grade II. Two of the antrectomy patients also subsequently required Roux-en-Y conversion for bile reflux, gastritis and vomiting, and are now Visick I and II, respectively The preoperative basal and maximal acid outputs in response to pentagastrin stimulation were recorded in 185 of the 305 patients (*Table 1*). In 47 patients in whom basal acid was above 6 mmol, the incidence of recurrent ulceration was 23 per cent, whereas in 138 patients with lower basal acids it was 16 per cent; this was not statistically significant. The 10-day postoperative insulin test proved a poor predictor of recurrent ulceration and was abandoned. Late insulin tests were performed on 26 patients with proven recurrences and 22 were positive in varying degrees (1^+–5^+)

The recurrent ulcer rate was also operator-dependent The two consultants had 28 recurrent ulcerations in 218 operations. The first consultant had three recurrences in 52 operations (6 per cent) while the second consultant had 25 recurrences in 166 operations (15 per cent). In the registrar-operated group, there were 18 recurrent ulcers in 87 operations (21 per cent). There was no statistical difference between these groups, either in relation to preoperative acid studies or recurrence rates

Of the 20 patients with recurrent ulcers not treated surgically, 12 are still on treatment with H_2-receptor antagonists.

Visick grading

Two hundred and thirty-five (77 per cent) of the 305 patients were satisfied with the results of the first operation and were graded Visick I and II (*Table 2*). Nineteen patients were graded Visick III, mainly because of unexplained abdominal pain; in this group no ulcer was found on endoscopy. Fifty-one patients were initially considered as Visick IV because of recurrent ulceration in 46, lesser curve necrosis in two, gastric retention in two and dysphagia in one patient who required transthoracic refundoplication because of recurrent hiatal herniation and reflux oesophagitis with stricture (*Table 3*). Following medical and surgical therapy, no patient in the series is now graded Visick IV. Two hundred and eighty (92 per cent) of the patients are now graded Visick I and II and are happy with the results of their operation (*Table 4*).

Discussion

It is now more than 20 years since the introduction of proximal gastric vagotomy without drainage for duodenal ulcer surgery.

Table 1 *Preoperative basal and maximal acid output in patients with and without ulcer recurrence*

	Basal acid output (mmol)	Maximal acid output (mmol)
Recurrence ($n=33$)	5·8 (0·3–18·2)	34·2 (2·2–82·6)
No recurrence ($n=152$)	4·3 (0·1–38·9)	32·1 (0·2–82·4)

Values represent mean; range is shown in parentheses

Table 2 *Initial results of proximal gastric vagotomy at 10–20-year follow-up*

Visick grade	No. of patients
I	150
II	85
III	19
IV	51
Total	305

Table 3 *Causes of failure in 70 patients*

Visick grade III	*n*	Visick grade IV	*n*
Unexplained abdominal pain	10	Recurrent ulcer	46
		Lesser curve necrosis	2
Oesophagitis	5	Gastric retention	2
Psychogenic	2	Reoperation for oesophageal stricture	1
Alcoholic	1		
Diarrhoea	1		
Total	19	Total	51

P 25,339

Table 4 *Corrected Visick grading for 302 patients*

Visick grade	No. of patients
I	181
II	99
III	22
IV	0
Total	302

*Three patients are not included as <1 year has elapsed since recurrence

Perhaps no other gastric operation has been followed up more carefully, especially since flexible endoscopy has been available throughout the lifetime of the operation. The safety of the procedure is unquestioned and its value in avoiding the unpleasant sequelae of drainage procedures is well established[8]. However, with longer periods of follow-up, the high recurrence rates being reported from some centres are disturbing. Most worrying was a report from one of the groups which produced the original description of the operation; they found a 39·3 per cent recurrence rate in a prospective randomized controlled trial of vagotomies, and concluded that: 'None of the three forms of vagotomy can be recommended as the standard operative treatment for duodenal ulceration'[6]. In that study from Copenhagen, the operation was performed for duodenal, pyloric and prepyloric ulcers, with 68 per cent of the operations being carried out by surgeons-in-training. The 15 per cent recurrence rate seen in this report refers to patients with duodenal ulceration only. Thirty per cent of the operations were carried out by surgeons-in-training, usually under supervision.

We have been gratified to find, as yet, no recurrent ulcer after the 13-year period and this has been the experience of others in the UK[9,10]. Although Hoffmann and colleagues noted no difference in recurrence rate whether the operation was carried out for duodenal or prepyloric ulcers, others have found a higher recurrence rate for the latter[5]. They are now asking: 'Is it time to ring the death knell for parietal cell vagotomy?' While the recurrent ulceration rate is significant, all recurrences should not be classified as failures. Presently available drugs allow control of recurrent ulceration without resort to operation in the majority of patients. Even ulcers which have previously proved resistant to medical therapy may become amenable to such treatment after parietal cell vagotomy[11]. Physicians do not give up when ulcers recur following medical therapy. For example, a 2-month course of an H_2-receptor antagonist heals 85 per cent of ulcers, but the majority recur within 1 year of ceasing the drug and, even on maintenance therapy, the relapse rate may be as high as 30 per cent per year[12].

Clinically significant gastric retention has not been a problem; it occurred in only two patients. Lesser curve necrosis in two of the 29 patients with combined proximal gastric vagotomy and fundoplication was worrying, and the anti-reflux procedure may have been a factor in this aetiology. However, Jordan has not encountered this problem in 115 patients in whom the combined procedure was used for reflux oesophagitis[13]. In this situation the authors now perform a short floppy fundoplication and decompress the stomach for a few days with a nasogastric tube.

The incidence of peptic ulcer disease declined during the decade before the introduction of H_2-receptor antagonists. As a result of the change in natural history and the availability of more potent drugs, fewer and fewer patients are being referred for elective surgery for duodenal ulceration. Since good results for proximal gastric vagotomy are operator-dependent, few surgeons are now gaining the necessary expertise in the technique. Amdrup suggests that surgeons need to perform at least ten operations per year to be proficient[14].

Primrose and colleagues feel that surgeons are now being referred a less favourable group of patients in whom a more intractable ulcer diathesis which is refractory to H_2-receptor antagonists is seen. In their series, the recurrent ulceration rate was much higher in patients resistant to drugs than in patients who responded to medical therapy[15]. Should we therefore proceed to truncal vagotomy and antrectomy for these drug-resistant patients? The evidence from Houston is that the recurrence rate for duodenal ulcer is similar whether one uses selective vagotomy and antrectomy or parietal cell vagotomy, but that the postoperative Visick grading is superior for the latter operation[16]. These workers did, however, exclude pyloric and prepyloric ulcers, for which there was a much higher recurrence rate after parietal cell vagotomy. It is often difficult to differentiate clearly between pyloric and duodenal ulcer in practice. Perhaps for the prepyloric ulcer in the undeterred smoker, vagotomy and antrectomy is the operation of choice. However, proximal gastric vagotomy is a good operation if performed for duodenal ulceration by a surgeon experienced in the technique. Should recurrent ulceration occur, the majority will respond to medical therapy. For those in whom therapy fails, truncal vagotomy and antrectomy may be carried out as a secondary procedure without undue difficulty. In this way one should be able to achieve a patient satisfaction rate of greater than 90 per cent. As Muller and colleagues have pointed out, the Visick grading 5 years after proximal gastric vagotomy is almost identical to that of healthy controls[17]. Proximal gastric vagotomy is not dead and should not be buried.

Acknowledgements

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Surgical workshop

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Formation of a loop stoma

A. Senapati and R. J. Nicholls

St. Mark's Hospital, City Road, London EC1V 2PS, UK
Correspondence to: Miss Asha Senapati

The satisfactory formation of a loop colostomy or ileostomy is largely dependent on the ability of the surgeon to pull a loop of bowel through a small defect in the anterior abdominal wall and hold it there without trauma. Traction forceps (such as Babcock forceps) can be pulled off the bowel, tearing it in the process. Damage to the mesenteric vessels can occur by dissection and insertion of the 'rod' beneath the loop after it has been pulled through. A simple atraumatic method of creating a loop stoma is now described.

The loop of bowel which can be brought to the surface without tension is identified. A small pair of artery forceps is used to create a small defect in the mesentery adjacent to the bowel wall between the mesenteric vessels, taking care not to damage them. A size 10 or 12 Jacques soft rubber catheter is threaded through the defect and passed through the hole in the anterior abdominal wall (*Figure 1*). The loop of bowel is then easily brought out to the exterior. The catheter is eased over the end of a Convatec™ (Uxbridge, UK) plastic stoma rod in which one end swivels to lie in the same vertical plane as the rod (*Figure 2*). The rod is then passed through the mesenteric defect (*Figure 3*), the catheter removed and the end swivelled to lie at a right angle flat on the anterior abdominal wall (*Figure 4*). Removal of the rod on the fifth day is very easy.

Acknowledgements

We would like to thank Miss Jill Maybee for the photographs and Convatec™ for financing the cost of printing them.

Paper accepted 2 June 1990

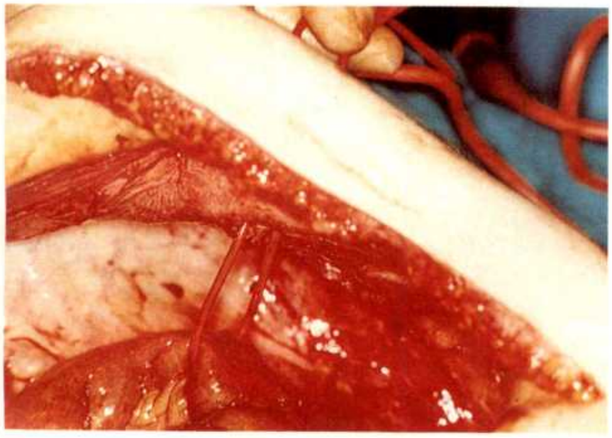

Figure 1 *A catheter is threaded through a mesenteric defect then passed through the hole in the anterior abdominal wall*

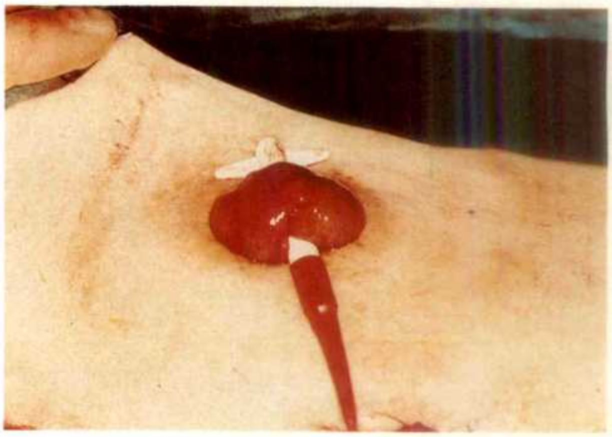

Figure 2 *The rod is passed through the mesenteric defect*

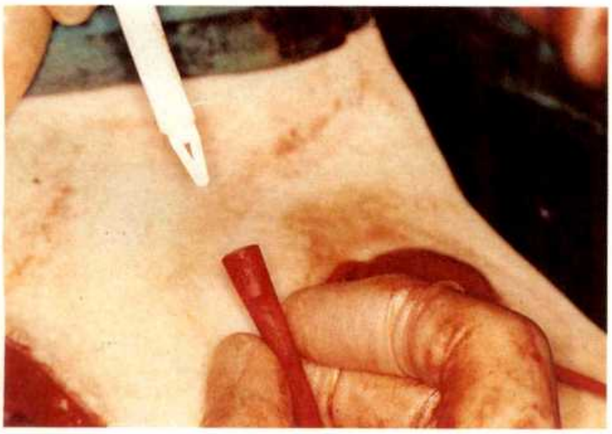

Figure 3 *The catheter is eased over the end of the stoma rod*

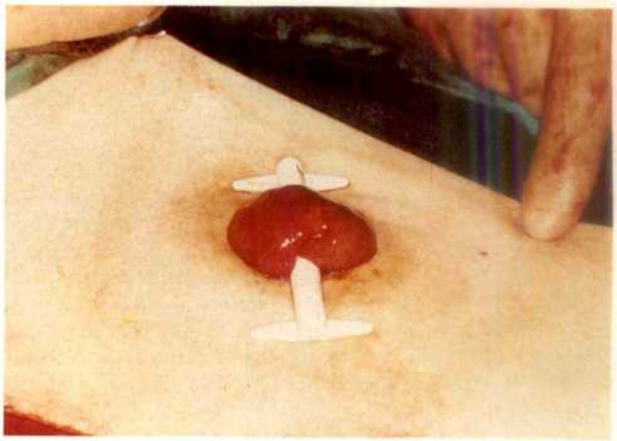

Figure 4 *The catheter is removed and the end swivelled to lie flat on the abdominal wall*

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24–27

Gastric adaptive relaxation and symptoms after vagotomy

Gastric adaptive relaxation is reported to be impaired after vagotomy. This abnormality has been implicated in the pathogenesis of postvagotomy symptoms, but no association has previously been demonstrated between the two. Gastric adaptive relaxation was measured in 15 healthy volunteers and 33 patients more than 1 year after highly selective vagotomy or truncal vagotomy and drainage. Seventeen patients were asymptomatic. The remainder were symptomatic including seven patients with persistent diarrhoea. Fasted subjects were intubated with a Ryle's tube containing a pressure microtransducer within a flaccid (800 ml) plastic bag. Gastric corpus–fundus pressure was recorded during distension of the bag with air (15 ml/s) over 30 s. Pressure indices were derived from the areas under the pressure curves. Median (range) pressure indices were: healthy volunteers 12·7 (7·5–17·1) cmH_2O, highly selective vagotomy 14·0 (9·8–15·9) cmH_2O (n.s.), truncal vagotomy and drainage 14·5 (8·6–26·8) cmH_2O ($P = 0{\cdot}04$). All patients with diarrhoea had abnormally high pressure indices ($P < 0{\cdot}001$). Pressure indices in all other patient groups were within the normal range. We conclude that gastric adaptive relaxation remains abnormal in patients with postvagotomy diarrhoea but not in those who are asymptomatic or who have other symptoms.

M. N. Hartley and
C. R. Mackie

University Department of Surgery,
Royal Liverpool Hospital, Liverpool
L7 8XP, UK
Correspondence to:
Mr C. R. Mackie, Department of
Surgery, Royal Liverpool Hospital,
PO Box 147, Liverpool L69 3BX, UK

Impairment of gastric adaptive relaxation has been reported after both truncal vagotomy[1–3] and highly selective vagotomy[4–7] and the degree of impairment is said to be similar after either operation[8,9]. Studies in both man and animals have been carried out after vagotomy, at laparotomy[9–11] and a few months later[1,2,4,6,8,12]. Few studies, however, have measured gastric adaptive relaxation more than 1 year after surgery.

The impairment of gastric adaptive relaxation, in combination with other motility disturbances after vagotomy, is implicated in the pathophysiology of postvagotomy symptoms. Symptoms after truncal vagotomy and drainage tend to be worse than after highly selective vagotomy. This has been attributed to the more disturbed gastric emptying associated with the drainage procedure and denervation of the antropyloric segment and the small bowel[13,14]. It is recognized, for example, that diarrhoea after highly selective vagotomy is uncommon, while after truncal vagotomy and drainage diarrhoea is frequently reported and may be a serious and persistent problem for a minority of patients[15].

The contribution of impaired gastric adaptive relaxation to the pathogenesis of postvagotomy disorders is both speculative and controversial. Postprandial epigastric fullness has been attributed to the failure of gastric adaptive relaxation[1,4]. Early rapid gastric emptying is thought to be the key abnormality causing the dumping syndrome and may also contribute to the pathogenesis of postvagotomy diarrhoea. Early rapid gastric emptying is thought partly to be due to impaired gastric adaptive relaxation[2]. There are, therefore, clinically recognized links between impairment of gastric adaptive relaxation and the presence of symptoms after vagotomy.

To date, there has been no study of gastric adaptive relaxation specifically comparing patients with and without symptoms after vagotomy. The aim of this study was to measure gastric adaptive relaxation in patients after highly selective vagotomy and truncal vagotomy and drainage in relation to their various symptoms more than 1 year after surgery. The study was formally approved by the Royal Liverpool Hospital Ethical Committee in November 1985. Written informed consent was given by all subjects studied.

Patients and methods

Fifteen healthy volunteers were studied (13 men and two women). Their median age and body-weight were 30 (range 22–41) years and 70 (range 50–79) kg. All healthy volunteers were asymptomatic on no medication. None had undergone any previous upper gastrointestinal surgery.

There were 33 patients in the study. All had previously undergone vagotomy for intractable duodenal ulceration, confirmed by endoscopy or barium meal and subsequently at laparotomy, or carried out for complications of duodenal ulcer. Twenty-five of the patients (20 men and five women) had had truncal vagotomy and drainage (18 pyloroplasty and seven gastroenterostomy) and eight patients, highly selective vagotomy (six men and two women). The median age and body-weight for patients in the truncal vagotomy and drainage group were 51 (range 35–67) years and 63 (range 44–92) kg. The median age and body-weight for patients in the highly selective vagotomy group were 35 (range 23–47) years and 77 (range 59–91) kg. The median time since operation was 4 years 6 months (range 1–24 years) for patients after truncal vagotomy and drainage and 2 (range 1–3) years for patients after highly selective vagotomy.

Five patients after highly selective vagotomy and 12 patients after truncal vagotomy and drainage were asymptomatic. Symptoms in the remaining patients, summarized in *Table 1*, had been present for over 1 year. Some symptomatic patients had more than one symptom. *Table 2* shows the nature and severity of diarrhoea in patients with this symptom. No patient had or gave a history of recurrent ulceration following vagotomy. All symptomatic patients had undergone routine investigation of their symptoms. All patients studied were systematically classified in terms of presence or absence, nature and severity of symptoms before undergoing the studies described.

The healthy volunteer and patient groups were studied in the same manner. The technique for measuring gastric adaptive relaxation was a modification of that used by Jahnberg *et al.*[3] and identical to that recently reported by our group[16]. After an overnight fast, subjects swallowed, via the nose, a 10 Fr Ryle's tube with a collapsed plastic bag (800 ml) sealed over the end, the side holes of the tube being within the bag. Within the lumen of the tube, positioned near the tip, was a

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Table 1 *Symptoms in patients after vagotomy*

	No of patients	Symptoms
Highly selective vagotomy	5	None
	3	Epigastric fullness
Truncal vagotomy and drainage	12	None
	5	Epigastric fullness
	3	Bilious vomiting
	2	Vasomotor dumping
	7	Diarrhoea

Table 2 *Characteristics of postvagotomy diarrhoea in seven patients after truncal vagotomy and drainage*

Diarrhoea		
Continuous/episodic	Stool frequency (maximum per day)	Urgency
Continuous	10	+
Continuous	6	+
Continuous	5	+++
Continuous	5	+++
Episodic	5	+++
Episodic	3	+
Episodic	2	++

Continuous, loose stools every day, episodic, loose stools at intervals of days or weeks, urgency: +, urge to defaecate; ++, precipitate urge to defaecate; +++, incontinent of faeces

pressure microtransducer (Gaeltec, Dingwall, Rosshire, UK) which was calibrated against a water manometer to provide a full scale deflection of 50 cm of water. The transducer was interfaced with an amplifier and pen recorder (Gould Electronics Ltd, Coventry, UK) to record pressure changes against time. The bag was positioned manometrically in the corpus–fundus of the stomach. A baseline recording was obtained during a 15 min rest period. Air from a compressed air cylinder (British Oxygen Company, Guildford, UK) was delivered at a constant rate via an air flow meter and a safety valve to the Ryle's tube. This constant flow of air was used to distend the bag at a rate of 15 ml/s for 30 s during which the pressure rise within the intragastric bag was recorded. The recording was continued at this end volume for a further 150 s. The air was then aspirated with a syringe and the volume noted. This procedure was repeated at 15 min intervals to provide four recordings for each subject, two each with subjects sitting and supine. For each recording a dynamic pressure index was derived from the area under the curve during distension. These measurements were ascribed units in cmH_2O (*Figure 1*) A single value was then derived for each subject by taking the mean of the four observations

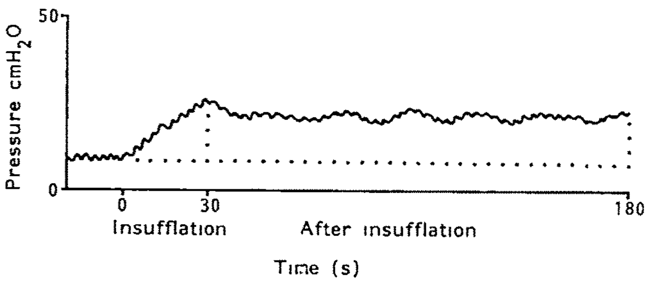
Statistical analyses of pressure indices between groups were made using the Kruskal–Wallis and Mann–Whitney *U* tests. Analysis of variance was used to compare volumes of air aspirated between groups. The χ^2 test was used to compare the types of drainage procedure.

Results

As previously reported[17] there was no identifiable trend of variation in successive recordings during individual studies. There was no detectable difference between sitting and supine recordings. All pressure indices in patients after highly selective vagotomy were within the range obtained for healthy volunteers (*Figure 2*). The median pressure index for these patients (14·0 cmH_2O) was higher than that for the healthy volunteer group (12·7 cmH_2O) but this difference was not statistically significant.

Pressure indices in patients after truncal vagotomy and drainage were significantly higher than those in the healthy volunteer group ($P=0{\cdot}04$). The median pressure index for patients after truncal vagotomy and drainage was 14·5 cmH_2O (*Figure 2*). When these patients were divided into asymptomatic and symptomatic groups, all of the asymptomatic patients had pressure indices within the range for healthy volunteers with a median pressure index of 13·8 cmH_2O (*Figure 3*). The median pressure index for the symptomatic patients after truncal vagotomy was 17·6 cmH_2O and this was significantly higher ($P<0{\cdot}025$) than both healthy volunteers and asymptomatic patients.

Further analysis of symptoms in relation to pressure indices



Dynamic pressure index = $\frac{\text{Area under curve during insufflation}}{30}$ cmH_2O

Figure 1 *Derivation of the dynamic pressure index from the pressure recording*

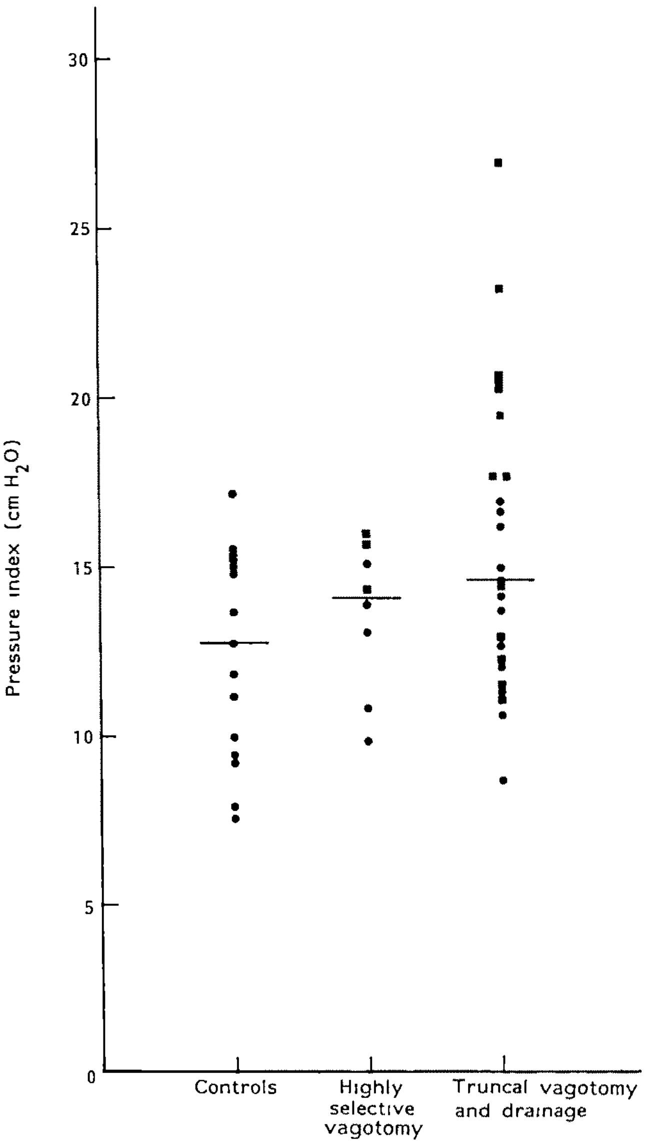


Figure 2 *Scattergram of pressure indices in healthy volunteers and patients after highly selective vagotomy and truncal vagotomy and drainage. Median values shown by bars* (●) *Asymptomatic,* (■) *symptomatic*

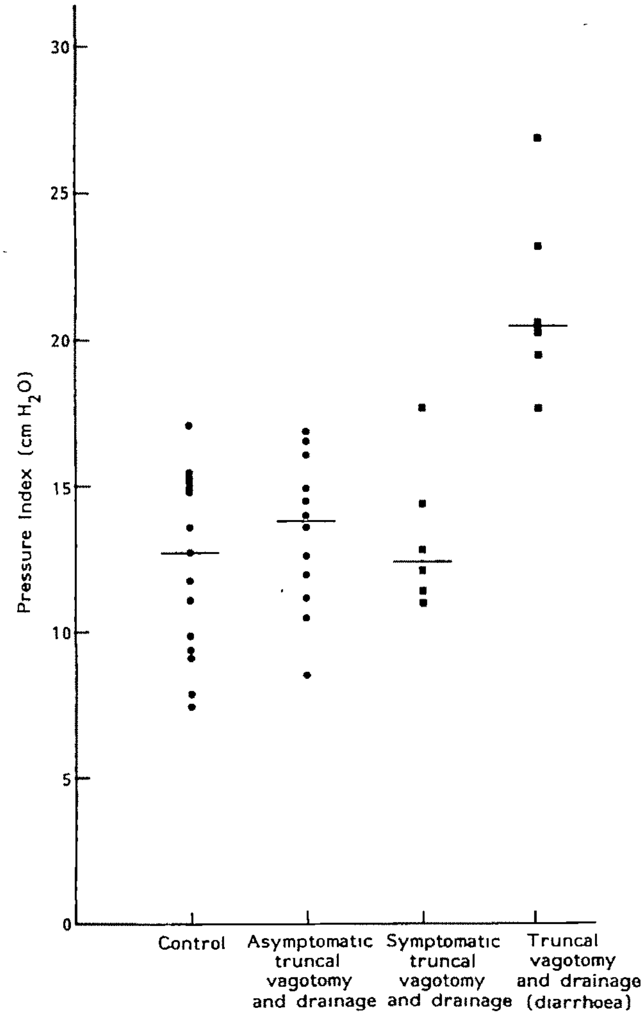


Figure 3 *Scattergram of pressure indices in healthy volunteers and asymptomatic and symptomatic patients after truncal vagotomy and drainage. Patients with postvagotomy diarrhoea are shown separately. Median values shown by bars.* (●) *Asymptomatic,* (■) *symptomatic*

revealed that patients with epigastric fullness tended to have higher pressure indices in both vagotomy groups; three patients with epigastric fullness in the highly selective vagotomy group were within the top four pressure indices of their group (*Figure 2*) and four of the five patients with epigastric fullness after truncal vagotomy had pressure indices above the range for healthy volunteers. The latter patients also had postvagotomy diarrhoea. Patients with bilious vomiting and vasomotor dumping had pressure indices within the range for healthy volunteers.

All seven patients with postvagotomy diarrhoea had pressure induces above the range for healthy volunteers. The median pressure index for the patients in this group was 20·3 cmH_2O. This value was significantly higher ($P<0{\cdot}001$) than the corresponding values for healthy volunteers, asymptomatic patients and symptomatic patients with symptoms other than postvagotomy diarrhoea (*Figure 3*).

The volume(s.d.) of air aspirates in all groups were the same (healthy volunteer group, 462(22) ml: highly selective vagotomy group, 465(17) ml: truncal vagotomy group, 456(20) ml).

Patients after truncal vagotomy and drainage were older ($P<0{\cdot}01$) than both the healthy volunteers and patients after highly selective vagotomy. Patients after highly selective vagotomy were heavier ($P<0{\cdot}05$) than both the healthy volunteers and patients after truncal vagotomy and drainage. The ages and body-weights of patients with and without postvagotomy diarrhoea, however, were not significantly different (51 years (median; range 39–67 years) and 65 (44–92) kg respectively).

There was no statistical correlation between the type of drainage procedure and the presence or absence of postvagotomy diarrhoea; four of 18 patients without diarrhoea and three of seven patients with diarrhoea had a gastroenterostomy.

Discussion

The method used to measure gastric adaptive relaxation was the same as that previously reported by our group[16]. We observed no significant change or identifiable trend of change in pressure indices with patients' posture during tests nor with successive insufflations at 15 min intervals during individual studies. Values for individuals have, therefore, been derived taking the mean of the four readings for each study. We have shown previously[17] that similar results may be obtained by analysis of pressure recordings obtained during the 2·5 min post-insufflation periods, before deflation of the bag, but these values tended to be less discriminatory. We have not, therefore, reproduced this analysis here. Our previously reported reproducibility studies showed good correlation ($r=0{\cdot}93$) between results from eight volunteers studied twice each on different days[16].

The control subjects were younger than patients after truncal the other two groups. In previous studies we found no correlation between age and gastric pressure response to distension[16]. We do not believe, therefore, that differences in the results obtained from the three groups can be accounted for by their age difference. Even if this were the case, our observations relating postvagotomy symptoms to high pressure responses would stand; there was no association between the age of patients and the presence of postvagotomy symptoms, nor has such an association been shown by others. Patients after highly selective vagotomy were heavier than subjects in the other two groups. There appeared to be no correlation between pressure indices and body-weight. In previous studies also, we were unable to demonstrate a correlation between body-weight and the gastric pressure response to distension[16]. Furthermore, there was no difference in age or body-weight between patients with and without diarrhoea.

Our results from patients with highly selective vagotomy would appear to indicate that gastric adaptive relaxation, as measured in this study, remains within the normal range at a year or longer following this operation. This finding is contrary to popular belief, but accords with previous observations made by others[5,6]. The casual critic might suggest that our test is insensitive in the lower pressure ranges and cannot discriminate between normal and slightly above normal pressure responses. Our previous demonstration of subnormal pressure responses among patients with gastro-oesophageal reflux[16] indicates that this is not so.

The above comments notwithstanding, we did observe a tendency for patients complaining of epigastric fullness after highly selective vagotomy to have higher pressure responses than asymptomatic patients in this group. The numbers of patients concerned, however, were too small to make a firm conclusion. A similar association between the complaint of epigastric fullness and higher pressure indices was suggested by results seen in patients with truncal vagotomy and drainage. It cannot be assumed that epigastric fullness is due to high intragastric pressure or gastric distension even though it is common for this explanation to be offered It could equally well be argued that epigastric fullness is due to volume or nutrient overloading of the upper small bowel. This is not inconsistent with observations on gastric emptying patterns after truncal vagotomy and highly selective vagotomy and would be in line with the incidental observation that epigastric fullness was not experienced by our subjects during the studies reported here, irrespective of the pressure responses obtained.

There were too few patients with bilious vomiting and dumping symptoms in the present study to make any firm conclusion. The recording of relatively low gastric pressure responses in patients with bilious vomiting is not surprising since duodenogastric reflux requires a reversed transpyloric pressure gradient to which a low intragastric pressure might contribute. The absence of high gastric pressure responses in patients with dumping symptoms is harder to explain. It should be remembered, however, that the rapid gastric emptying seen in patients with dumping may be partly due to pyloric incompetence and disturbed duodenojejunal motility resulting in diminished resistance to filling exhibited by the upper small bowel. The rarity of dumping symptoms after highly selective vagotomy and the efficacy of pyloric reconstruction for the treatment of dumping are in keeping with this hypothesis.

The most striking finding in the present study was the consistently high gastric pressure response to distension observed in patients with postvagotomy diarrhoea. All patients with this symptom exhibited pressure indices above the range for healthy volunteers and the difference between this group of patients and all other groups was statistically highly significant. There is evidence that patients with postvagotomy diarrhoea have more rapid gastric emptying than patients who are asymptomatic after similar operations[18] and the results of the present study suggest that rapid gastric emptying in patients with diarrhoea is partly due to impaired gastric adaptive relaxation. It seems unlikely, however, that rapid gastric emptying due to failure of gastric adaptive relaxation alone can explain the presence of this symptom. Rapid small bowel transit and perhaps a disturbance of colonic motility may constitute factors of equal or greater pathogenic importance. Whether the gastric abnormality revealed in this study triggers abnormal downstream function or merely reflects a greater degree of total gut disturbance in these patients remains a moot point. The fact that all patients with postvagotomy diarrhoea showed impaired gastric adaptive relaxation while symptoms were noted to be episodic in three of the patients, may have been a chance observation or may be taken to point to the second explanation. It should be noted that no patient with post-vagotomy diarrhoea in the present study also complained of significant dumping symptoms yet the co-existence of dumping and diarrhoea is quite common in clinical practice. For the moment we must assume that patients with both symptom complexes have postvagotomy disturbances that are common to the pathophysiology of both complaints.

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Peptic ulcer surgery during the H_2-receptor antagonist era: a population-based epidemiological study of ulcer surgery in Helsinki from 1972 to 1987

H. Paimela*, P. K. Tuompo*, T. Peräkylä‡, I. Saario†, K. Höckerstedt‡ and E. Kivilaakso§

*Departments of Surgery, *Malmi and †Maria Helsinki City Hospitals and §Second and ‡Fourth Departments of Surgery, Helsinki University Central Hospital, Helsinki, Finland*

Correspondence to:
Mr H. Paimela, Second Department of Surgery, Helsinki University Central Hospital,
Haartmaninkatu 4, SF-00290
Helsinki, Finland

To evaluate the effects of improvements in medical therapy on the incidence of, indications for and operative methods used in peptic ulcer surgery, all cases of primary peptic ulcer surgery among adults in the city of Helsinki in the years 1972, 1977, 1982 and 1987 were analysed. There was a total of 565 such cases in a population which consisted of $5{\cdot}2 \times 10^5$ *individuals in 1972 and* $4{\cdot}8 \times 10^5$ *individuals in 1987. The introduction of* H_2*-receptor antagonists in 1979 was associated with a fall in the annual incidence of elective duodenal ulcer operations, from 15·5 to 6·7 per* 10^5 *individuals, and a fall in the annual incidence of elective gastric ulcer operations, from 9·4 to 3·1 per* 10^5 *individuals* ($P < 0{\cdot}05$)*. The decrease was greatest among males with duodenal ulcer. In contrast, the annual incidence of emergency surgery for ulcer haemorrhage and perforation (all types of ulcers) remained relatively stable, varying from 7·2 to 10·2 per* 10^5 *inhabitants over the observation period (n.s.). The mean age of patients undergoing elective surgery remained essentially unchanged. The mean age of patients undergoing emergency surgery increased. The decrease in the annual incidence of elective duodenal ulcer surgery occurred mainly in relation to proximal gastric vagotomy. There was a concomitant relative increase in the incidence of gastric resection. The types of operative procedures used in cases of pyloric, prepyloric and gastric ulcer remained unchanged over the years 1972 to 1987.*

Important advances in peptic ulcer surgery following the introduction of partial gastrectomy have included truncal vagotomy, first reported in 1943 by Dragstedt and Owens[1], selective vagotomy, first reported in 1957 by Griffith and Harkins[2], and parietal cell vagotomy, the most recent form, introduced in 1970 by Amdrup and Jensen[3] and Johnston and Wilkinson[4]. The introduction of highly selective vagotomy, an operation not interfering with gastroduodenal continuity, led to a widening of indications for peptic ulcer surgery, and to a disproportionate increase in elective peptic ulcer surgery. However, concomitant advances in the medical therapy of peptic ulcer disease, allowing efficient inhibition of acid secretion, have changed the management of peptic ulcer disease. The role of surgery has significantly decreased[5–8].

The study reported here aimed to evaluate the incidence and nature of the surgical treatment of peptic ulcer disease in Helsinki, Finland, with particular emphasis on assessment of the impact of the improvements in medical therapy on surgical treatment. The study involved a retrospective evaluation of all primary ulcer operations among Helsinki residents from 7 years before until 7 years after the introduction of H_2-receptor antagonists in Finland. The first such drug, cimetidine (Tagamet®, Smith Kline and French Laboratories Ltd., Welwyn Garden City, UK), was approved for marketing in Finland in January 1979.

Patients and methods

All primary operations for peptic ulcer disease in the years 1972, 1977, 1982 and 1987 were evaluated (chronological operating department diaries and patient records) in the four hospitals (Second and Fourth Departments of Surgery, Helsinki University Central Hospital and the Departments of Surgery in Malmi and Maria Helsinki City Hospitals) responsible for the surgical treatment of peptic ulcer disease in adults in Helsinki. It was found that there had been 565 primary ulcer operations in a population varying from $5{\cdot}2$–$4{\cdot}8 \times 10^5$ people over the observation period. Diagnoses had been verified by barium meal or endoscopy, or during operation. Patients operated on for haemorrhagic gastritis, erosive gastritis or acute superficial ulcer were excluded, as were patients with upper gastrointestinal bleeding of unconfirmed aetiology, even though typical ulcer surgery had been performed.

One-way analysis of variance, Student's t test for unpaired observations, and the χ^2 test were used for statistical analysis of the findings.

Results

Demographic changes

Population. The number of adult inhabitants in Helsinki decreased over the period of observation from 519 508 in 1972 to 488 604 in 1987.

Age and sex. The percentages of those over 65 years of age were 10·5 in1972 and 14·4 in 1987 (n.s.). The female/male ratio remained constant (1·0·8) over the period of observation.

Percentages of ulcer operations. Operations for peptic ulcer accounted for 1·9 per cent of all operations in the four surgical units in 1972, for 3·5 per cent of all operations in 1977, for 2·2 per cent of all operations in 1982 and for 1·5 per cent of all operations in 1987 (n.s.).

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Emergency surgery

Perforation. Operation for duodenal (bulbar) ulcer perforation was undertaken in 1972 in 2·3 per 10^5 Helsinki adult inhabitants, in 1977 in 1·2 per 10^5, in 1982 in 1·3 per 10^5 and in 1987 in 2·0 per 10^5 (n.s.). Operation for prepyloric and pyloric ulcer perforation was undertaken in these years in 1·3, 1·4, 2·3 and 1·8 per 10^5 inhabitants, respectively (n.s.). Operation for gastric ulcer perforation was undertaken in 1·3, 1·4, 0·6 and 1·2 per 10^5 inhabitants (n.s.), respectively.

The total number of operations for ulcer perforation performed annually ranged from 4·0 to 5·0 per 10^5 inhabitants in the 4 years studied (n.s.) (*Figure 1*).

Haemorrhage. Emergency operation for duodenal ulcer haemorrhage was undertaken in the years 1972, 1977, 1982 and 1987 in 1·5, 1·4, 2·1 and 1·4 per 10^5 inhabitants, respectively (n.s.). The corresponding values for prepyloric or pyloric ulcer haemorrhage were 0·6, 0·4, 0·6 and 0·2 per 10^5 inhabitants (n.s.). For gastric ulcer haemorrhage they were 1·9, 1·2, 1·5 and 1·4 per 10^5 inhabitants (n.s.).

The total number of operations for ulcer haemorrhage performed annually ranged from 3·0 to 4·2 per 10^5 inhabitants in the 4 years studied (n.s.) (*Figure 2*).

Gastric outlet obstruction. The incidences of operation for manifest gastric outlet obstruction because of pyloroduodenal ulcer was 0·4 per 10^5 in 1972 and 1977, and 1·0 per 10^5 in 1982 and 0·2 per 10^5 in 1987 (n.s.).

Age and sex. The mean age of patients who underwent emergency surgery increased for each type of ulcer between 1972 and 1987 (n.s.). The mean age of patients with gastric ulcer perforation was higher than the mean age of patients with (pre)pyloric or duodenal ulcer perforation (n.s.) (*Table 1*). Among duodenal ulcer patients, the female/male ratio decreased significantly, from 1:2·0 in 1972 to 1:5·0 in 1982; it then increased again to 1:1·7 in 1987 ($P<0{\cdot}05$). Among pyloric or (pre)pyloric ulcer patients, the ratio increased from 1:6·0 in 1972 to 1:1·3 in 1987 ($P<0{\cdot}05$). Among gastric ulcer patients, the female/male ratio changed from 1:0·9 in 1972 to 1:3·7 in 1987 (n.s.).

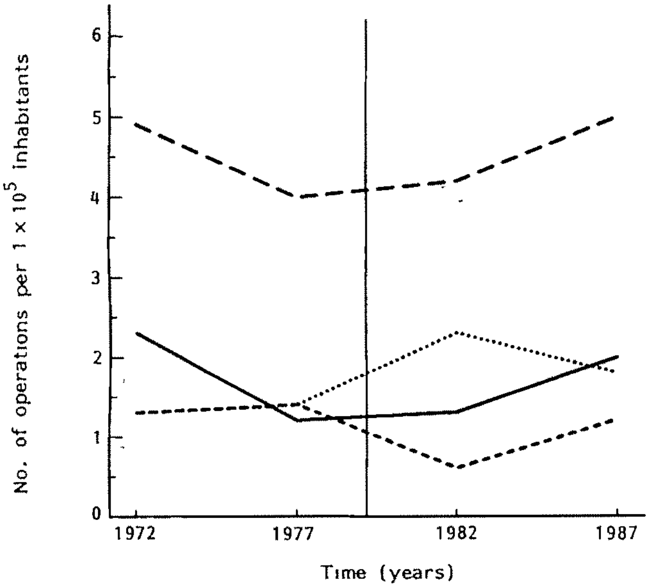

Figure 1 *Operation for peptic ulcer perforation among adult residents of Helsinki in 1972, 1977, 1982 and 1987. Duodenal ulcer (——), gastric ulcer (–––), (pre)pyloric ulcer (· · · ·), all ulcer types (– – –) (n.s. for all) H_2-receptor antagonists started (——)*

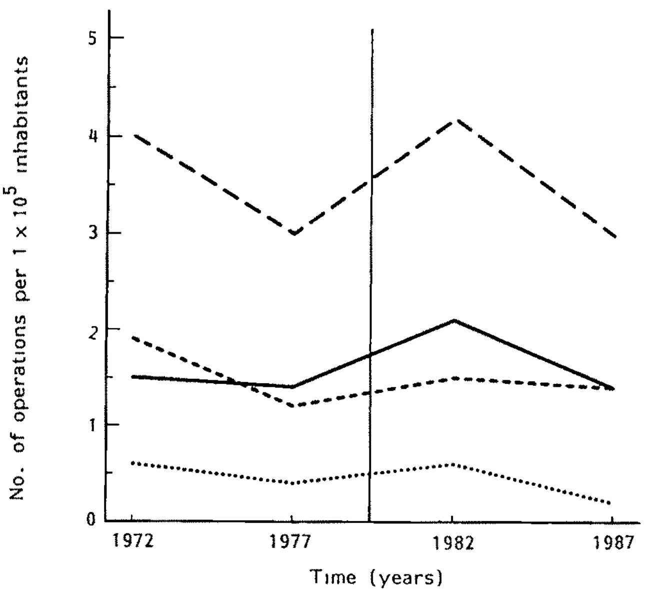

Figure 2 *Operation for peptic ulcer haemorrhage among adult residents of Helsinki in 1972, 1977, 1982 and 1987. Duodenal ulcer (——), gastric ulcer (–––), (pre)pyloric ulcer (· · · · · ·), all ulcer types (– – –) (n.s for all). H_2 -receptor antagonists started (——)*

Table 1 *Mean ages (in years) of patients undergoing emergency operations*

	Year			
	1972	1977	1982	1987
Duodenal ulcer	55·8(3·6)	51·7(3·4)	52·7(4·5)	60·4(4·6)
(Pre)pyloric ulcer	48·8(4·5)	58·0(5·4)	54·4(4·9)	52·7(5·9)
Gastric ulcer	59·3(3·4)	62·5(4·0)	60·0(5·8)	63·7(4·5)

Values are mean(s.e.m.). One way analysis of variance, all changes not significant

Elective surgery

Duodenal ulcer. In 1972, elective surgery for duodenal ulcer was undertaken in 9·2 per 10^5 inhabitants. In 1977, the incidence of surgery was 15·5 per 10^5, in 1982 it was 12·3 per 10^5 and 6·7 per 10^5 in 1987 ($P<0{\cdot}05$) (*Figure 3*).

The relative incidence of proximal gastric vagotomy increased significantly from 1972 (when it accounted for 9 per cent of all duodenal ulcer operations) to 1977 (when it accounted for 74 per cent of all duodenal ulcer operations). It decreased to 52 per cent in 1987 ($P<0{\cdot}05$). These changes occurred mainly because the incidence of vagotomy and pyloroplasty fell. Vagotomy and antrectomy accounted for 54 per cent of all elective duodenal ulcer operations in 1972 but only 36 per cent in 1987 (n.s.) (*Figure 4*).

Pyloric and prepyloric ulcer. Elective surgery for pyloric and prepyloric ulcer was undertaken in 4·2 per 10^5 inhabitants in the year 1972 but in only 1·2 per 10^5 inhabitants in 1987 (n.s.) (*Figure 3*).

In prepyloric or pyloric ulcer, the operative procedure was vagotomy and antrectomy in 90 per cent of instances in 1972 and in 66 per cent of instances in 1987 (n.s.). There was no instance in which proximal gastric vagotomy was undertaken for pyloric or prepyloric ulcer in 1972. In 1987 it was undertaken in 34 per cent of cases ($P<0{\cdot}05$).

Gastric ulcer. Elective surgery for gastric ulcer was undertaken in 9·4 per 10^5 inhabitants in 1972. The incidence was only 3·1 per 10^5 inhabitants in 1987 ($P<0{\cdot}05$) (*Figure 3*).

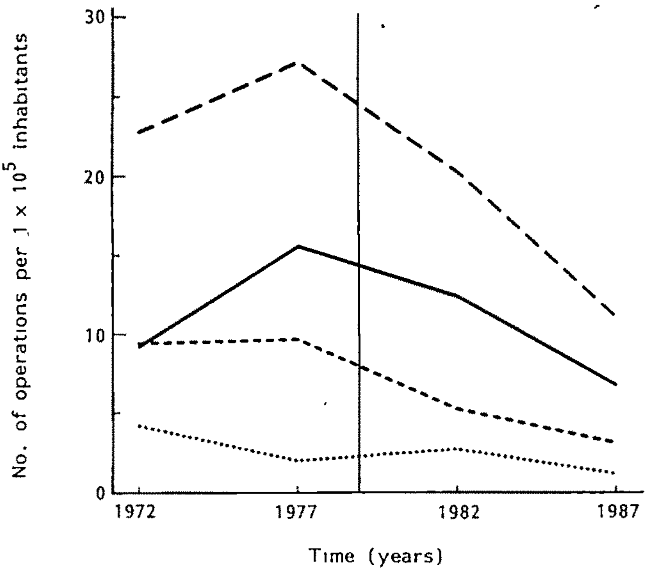

Figure 3 *Elective operation for peptic ulcer among adult residents of Helsinki in 1972, 1977, 1982 and 1987. Duodenal ulcer* (——), P<0 05, *gastric ulcer* (-----), P<*0·05; (pre)pyloric ulcer* (· · · · ·), *not significant, all ulcer types* (– – –), P<*0·05. H_2-receptor antagonists started* (——)

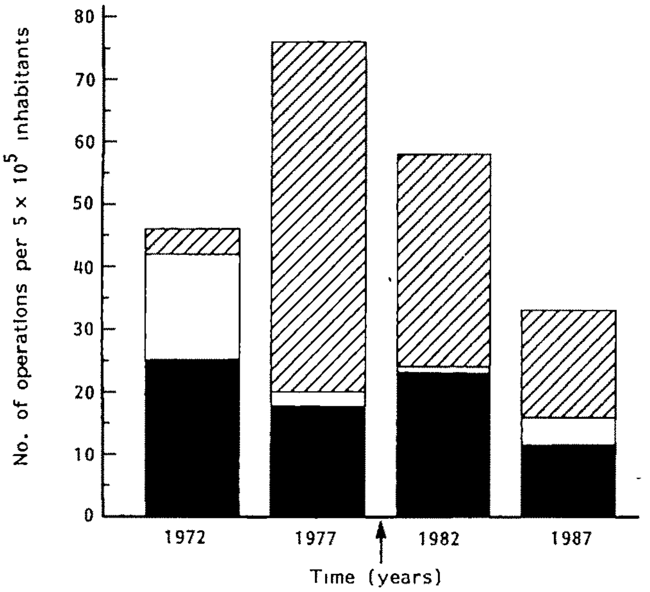

Figure 4 *Procedures used in primary operations for duodenal ulcer in adult residents of Helsinki in 1972, 1977, 1982 and 1987.* ■, *parietal cell vagotomy* (P<*0·05*); □, *vagotomy plus pyloroplasty* (P<*0·05*); ■, *vagotomy plus antrectomy* (*not significant*). *H_2-receptor antagonists started* (*arrow*)

In gastric ulcer, partial gastrectomy was the only operative procedure used in 1982 and 1987. However, in 1972 and 1977 some lesser procedures were used in 2 and 4 per cent of cases, respectively.

The total incidence of cases of primary elective operation for uncomplicated peptic ulcer was 22·8 per 10^5 in 1972, 27·1 per 10^5 in 1977, 20·2 per 10^5 in 1982 and 11·0 per 10^5 adult inhabitants of Helsinki in 1987 ($P<0·05$) (*Figure 3*).

Age and sex. The mean age of patients with duodenal and gastric ulcer undergoing elective surgery did not change, but in pyloric or prepyloric ulcer patients it increased over the period of observation. The mean age of patients with a pyloric or prepyloric lesion was higher than that of the rest of ulcer patients at the end of period of observation (n.s.) (*Table 2*).

Among those undergoing elective surgery, the female/male ratio among duodenal ulcer patients changed from 1:4·2 in 1972 to 1:1·5 in 1987 ($P<0·05$). Among patients with pyloric or prepyloric ulcer, the percentage of male patients also decreased. Among patients with gastric ulcer, the percentage of male patients increased during the observation period (n.s.).

Discussion

Concomitantly with developments in peptic ulcer surgery, leading from partial gastrectomy to parietal cell vagotomy, medical treatment of the disease has significantly improved. Using therapy with H_2-receptor antagonists, acid secretion from parietal cells can be inhibited as effectively as with vagotomy. However, it has been shown that this has had a relatively small influence on the epidemiology of peptic ulcer disease. The decline in the prevalence of the disease and in its surgical treatment had already started before the introduction of H_2-receptor antagonists[9,10]. These results are based on longitudinal studies in populations in the Rochester (Minnesota) area of the USA, and in Sweden. The study reported here assessed the incidence of peptic ulcer surgery in Helsinki in relation to the introduction of H_2-receptor antagonists.

In a recent epidemiological study of the residents in Gothenburg from 1985, the incidence of duodenal ulcer was found to be almost 2 per 10^3 inhabitants aged 60 years. The incidences of gastric and prepyloric ulcer were about 1 per 10^3 inhabitants aged 60 years[11]. The incidence of ulcer disease increased with age and was almost the same in both sexes. It is known from studies by Siurala *et al.*[12] that progression of chronic gastritic changes with age leads to a decrease in the number of fundic glands responsible for gastric acid secretion. It is also known that gastric acid secretion capacity is higher in men than in women[13]. The characteristics of hypersecretion of acid and male preponderance among those with peptic ulcer disease recorded previously seem to be no longer evident, especially in relation to pyloroduodenal ulcer.

The study reported here indicated that the incidence of the main complications of ulcer disease, perforation and haemorrhage, have remained unchanged. Their occurrences have been unaffected by the introduction of H_2-receptor antagonists. The annual incidence of emergency operations in the study reported here, 7·0–10·2 per 10^5 adult inhabitants of Helsinki, was slightly lower than that reported for residents of Rochester in USA, by Gustavsson *et al.*[9]. The mean ages of patients requiring emergency operations in the present study also increased. This may have been a result of prolonged conservative treatment, but could also have resulted from the general increasing of the percentage of elderly people in the population. The incidence of ulcer perforation, which best reflects the epidemiology of ulcer complications, occurred with a constant annual incidence of 4·0–5·0 per 10^5 inhabitants over the observation period. This incidence is slightly lower than that reported for Rochester[9]. Having regard to the recently reported incidence of active peptic ulcer among 60-year-old residents of Gothenburg (i.e. slightly over 1 per 10^3) it would seem that 4–5 per cent of active ulcers perforate during current medical therapy of peptic ulcer disease[11].

One may speculate that one reason for the constant frequency of the appearance of ulcer complications despite the decreased incidence of ulcer disease in general is the increased proportion of ulcer patients who, because of the reduction of

Table 2 *Mean ages (in years) of patients undergoing elective surgery*

	Time			
	1972	1977	1982	1987
Duodenal ulcer	48·6(2·2)	45·8(1·5)	45·9(1·6)	46·9(2·1)
(Pre)pyloric ulcer	49·4(2 8)	54·5(4·4)	61·4(3·6)	57·0(1·8)
Gastric ulcer	56·5(1·4)	57·2(1·7)	56 5(2·1)	49·6(4·4)

Values are mean(s.e.m.). One way analysis of variance, all changes not significant elective surgery, are on medical therapy. Although the ulcer diathesis may be temporarily suppressed in these patients, their ulcer disease has not been eradicated. Presumably, these patients with active (but suppressed) ulcer disease are still prone to ulcer complications.

While the annual incidence of emergency operation has remained essentially unchanged, the incidence of elective operation for ulcer has fallen significantly in Helsinki, primarily because of a decline in vagotomy and primarily in male duodenal ulcer patients. The findings of the study reported here supports the observations of Gustavsson *et al.*[9] concerning different epidemiological characteristics of elective and emergency ulcer surgery cases. The incidence of elective operation for peptic ulcer in the study reported here in the year 1987 ($11{\cdot}0 \times 10^5$ adult Helsinki inhabitants) was very similar to that in inhabitants of Rochester, USA[9]. In contrast, the annual incidence of operation of $22{\cdot}8 \times 10^5$ adult Helsinki inhabitants in 1972 was lower than that in Rochester ($25{\cdot}2 \times 10^5$ inhabitants). Whether this indicates a higher incidence of ulcer disease in Rochester than in Helsinki or whether there was a greater readiness to operate in Rochester cannot be determined on the basis of the data available.

The recent decrease in incidence of elective ulcer surgery in Helsinki was preceded by a significant increase in incidence of elective surgery, especially parietal cell vagotomy, between 1972 and 1977. This probably reflected a change in the indications for operation, which were likely to have become wider as a result of the introduction of a new, more conservative, operative method. After the introduction of H_2-receptor antagonists, most patients of this kind will, however, have been treated medically, resulting in the significant decrease in incidence of elective ulcer surgery. However, the absence of any significant change in incidence of partial gastrectomy suggests that the incidence of the more severe forms of the disease has not altered. It is possible that medical therapy only postpones the need for surgery in certain patients and that when surgery is needed partial gastrectomy, often on an emergency basis, is mandatory. Thus, despite the decrease in incidence of elective surgery, the relative incidence of resective duodenal ulcer surgery is increasing. The low numbers of patients with manifest gastric retention in the study reported here is probably explained by the transient nature of the disturbance. With modern medical therapy, the inflammatory process around the ulcer can often be alleviated and the obstruction and retention temporarily relieved, and the patients then move to the elective surgery group. Such patients are impossible to identify in this kind of retrospective study. Alternatively, it is possible that the nature of ulcer disease has become less severe, in accordance with general epidemiological developments.

The results of the study reported here indicate that the introduction of H_2-receptor antagonists has significantly decreased the incidence of elective peptic ulcer surgery, in particular parietal cell vagotomy, for duodenal (bulbar) ulcer, but that the incidence of emergency operation has remained unchanged, despite the improvements in medical therapy.

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Study of belching ability in antireflux surgery patients and normal volunteers

D. Smith, N. A. King, B. Waldron, P. T. Cullen, B. Millar*, M. Fenwick* and F. C. Campbell

*Departments of Surgery and *Medical Physics, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK*

Correspondence to:
Mr F C. Campbell

The ability to belch was evaluated by a novel test, after gaseous stomach distension to standard volume, in 16 patients after antireflux surgery and nine healthy volunteers. A structured assessment of dyspeptic symptoms was also carried out in both groups. Repeat studies in volunteers showed acceptable reproducibility for the new test of belching capacity (within-subject coefficient of variance 4·5 per cent). After antireflux surgery, patients had lower volume individual belches (median(range) 27·5(0–104) ml in patients versus *76(15–165) ml in volunteers;* P<0·02*) and belched less gas within 1 h of the stimulus than volunteers (median(range) 205(0–1363) ml in patients* versus *456(45–818) ml in volunteers:* P<0·05*). Belching frequency was similar in both groups. The incidence and severity of symptoms were unrelated to belched gas volumes.*

The effect of antireflux surgery on acid reflux[1] and lower oesophageal sphincter characteristics[2] has been well documented, but its influence on gas reflux or belching ability has received less attention. Belching ability, however, may be related to postoperative dyspeptic symptoms[3,4].

This study has evaluated belching ability in a consecutive series of antireflux surgery patients and volunteers, using a novel test. A structured assessment of dyspeptic symptoms was also carried out in both groups.

Patients and methods

Subjects

Sixteen patients entered the study, of whom 14 were women; their median age was 53 years (range 25–83 years). All patients had preoperative diagnosis of acid reflux established by 24-h oesophageal ambulatory pH monitoring and manometry.

Oesophageal pH monitoring was assessed using a pH-sensitive radiotelemetry pill suspended 5 cm above the manometrically determined high-pressure zone. Data were recorded using a portable microprocessor receiving unit (Aspen Medical Ltd., Ross-shire, UK) and analysis of the data gave the mean time of oesophageal pH <4, the mean number and duration of reflux events in both the erect and supine position, and the cumulative acid exposure expressed as the percentage of data below each pH unit from 3 to 6 during the study. An individual record was considered abnormal (positive for acid reflux) if any one parameter was >3 standard deviations outside the mean of a control group as previously described[5,6]. All patients were found by manometry to be free of clinical oesophageal motility disorders. Twelve of the patients had a Nissen fundoplication and four had a Belsey procedure performed, 1–3 years before the present study.

The nine volunteers (four women) had a median age of 21 years (range 21–35 years), were asymptomatic and received no regular medication. A gas pump then directed the belch/expired air mixture to a Rigel CO_2 monitor (P.K. Morgan Ltd., Chatham, UK) for measurement of carbon dioxide concentration. All studies were performed with the subjects in the erect position. All belched gas was collected and measured for 1 h after administration of the reagents, although few belches occurred after the first 10 min. The total volume of carbon dioxide belched within 1 h was calculated as the sum of all individual belches.

Test for the measurement of gastro-oesophageal gas reflux

This test is based on the measurement of belched gas volumes, after induction of gaseous stomach distension to a standard volume of 1200 ml. Gaseous stomach distension was achieved after an overnight fast by the oral administration of 4 g citric acid in solution, followed in rapid succession by 4 5 g sodium bicarbonate in solution, which liberates 1200 ml carbon dioxide in <30 s. These doses were calculated by the formula·

$$\begin{array}{lllll}
3NaHCO_3 & +C_6H_8O_7H_2O & \rightarrow C_6H_5Na_3O_7 & +4H_2O & +3CO_2 \\
252\ g & +210\ g & \rightarrow 258\ g & +72\ g & +132\ g \\
4\ 5\ g & +3{\cdot}75\ g & \rightarrow 4\ 6\ g & +1{\cdot}2\ g & +2\ 32\ g
\end{array}$$

(2·32 g carbon dioxide has a volume of 1200 ml at room temperature).

Each belch was collected into a 2·2 litre closed container system Subjects were instructed to avoid loss of gas through the nose and voluntary suppression of belches. All subjects were requested to belch through their mouths, when they felt the desire to do so, into the firmly applied mouthpiece of the container After each belch, the subject inflated the container to capacity with expired air (*Figure 1*).

Determination of belched gas volumes

Belched gas volumes were calculated from carbon dioxide concentrations, measured by the Rigel CO_2 monitor Background carbon dioxide measurements were taken of expired air before and after each study. All subjects belched into the closed container then filled the system to capacity with expired air. After each belch, the carbon dioxide concentration of the combined belch and expired air mixture was measured and carbon dioxide volumes were calculated as follows. The amount of carbon dioxide in the system after the belch and filling with expired air is C_xV, where C_x is the belch and expired air carbon dioxide concentration and V is the volume of container (2200 ml) C_xV is the sum of the carbon dioxide from the belch and the carbon dioxide from the expired air.

Therefore

$$C_xV = C_bV_b + C_eV_e$$

where C_b is the belched gas carbon dioxide concentration, V_b the volume of belch, C_e the expired air carbon dioxide concentration and V_e the volume of expired air.

But $V_e + V_b = V$ and, assuming that the belched gas is 100 per cent carbon dioxide, i.e. $C_b = 1$,

$$C_xV = V_b + C_e(V - V_b)$$

Hence, rearranging the equation,

$$V_b = \frac{V(C_x - C_e)}{1 - C_e}$$

Test reproducibility

The reproducibility of the test was assessed against total volumes of belched gas collected for 1 h after administration of the reagents in nine healthy controls. The test was repeated on three occasions.

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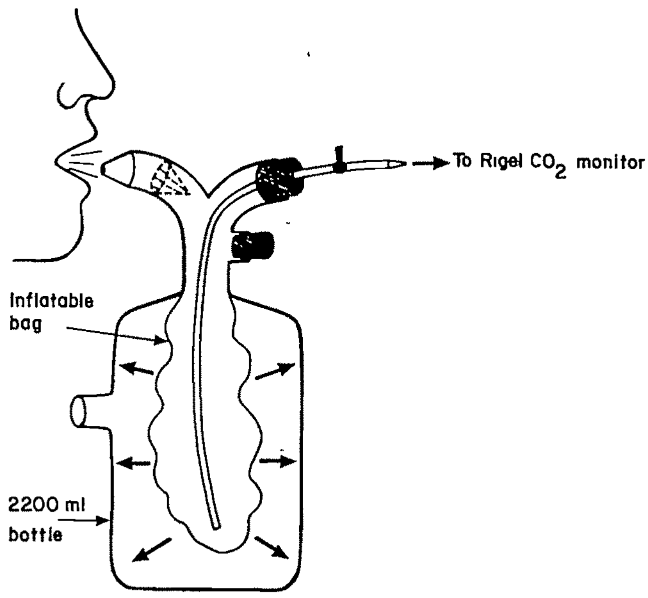

Figure 1 *Diagram of the closed container system*

Evaluation of belched gas volumes in patients and volunteers

Belched gas volumes were assessed by the described method in 16 of 22 consecutive patients who had undergone antireflux surgery in Ninewells Hospital between 1985 and 1987 and a second group of nine healthy volunteers. A structured assessment of 'gas bloat' type symptoms was carried out in patient and volunteer groups by scored questionnaire[7].

Symptom evaluation

Five dyspeptic symptoms that may occur after antireflux surgery were scored, namely postprandial fullness, swelling of the abdomen, urge to vomit, feeling unable to vomit, and feeling unable to belch[3]. Severity, frequency and duration of each symptom were scored on the model of Bates and Sjoden[7] on a scale of 0–4.

Severity. 0 = absent; 1 = present, not troublesome, 2 = slight trouble, 3 = moderate trouble; 4 = major trouble.
Frequency. 0 = absent; 1 = 1–2 times per week, 2 = 3–6 times per week; 3 = 1–3 times per day; 4 = more than 3 times per day.
Duration: 0 = absent, 1 = lasts < 10 min; 2 = lasts 10–30 min; 3 = lasts 31–60 min; 4 = lasts more than 60 min.

For each individual symptom, the score recorded was the sum of three values for severity, frequency and duration. This symptomatic assessment was referable to the subject's normal daily activities and was carried out at different times from the tests of gas reflux.

Ethical considerations

Ethical permission was granted by the Tayside Health Board Ethical Committee. Written permission was obtained from all participants and it was emphasized to the patients that the study was for research purposes only.

Data analysis

The Mann–Whitney *U* test was used to evaluate differences in the total volume belched and the volume per belch, between patients and volunteers. Kendall's rank correlation was used to evaluate the relationship between the symptom score with total volume belched and volume per belch. The components of variance were analysed and the within-subject coefficient of variation was derived from the equation[8]:

$$\text{Coefficient of variation} = \frac{\sqrt{\text{Mean within-subject variance}}}{\text{Overall mean total belch volume}}$$

Results

Test evaluation

The concentration of carbon dioxide in expired air (C_e) showed little variation (*Table 1*). In reproducibility studies, little within-individual variation in belched gas volumes was observed (coefficient of variation 4·5 per cent) (*Figure 2*) and differences between individuals were similar in all three studies.

Patient and volunteer studies

All volunteers were asymptomatic, but symptom scores in patients ranged from 0 to 44 (median 19). The most frequent symptoms were postprandial fullness and abdominal swelling (*Table 2*).

Patients belched lower volumes than volunteers, including individual belch volumes (median(range) 27·5(0–104) ml *versus* 76(15–165) ml, $P < 0·02$ (*Figure 3*) and total gas volumes within 1 h (median(range) 205(0–1363) ml *versus* 456(45–818) ml, $P < 0·05$ (*Figure 4*). Belching frequency was similar in both groups. Symptom scores, however, were unrelated to either individual belch volumes of carbon dioxide or total volume of carbon dioxide belched within 1 h (*Figure 5*).

Discussion

Belching of gas from the stomach is important because it limits the amount of swallowed air passing through the gastrointestinal tract and hence may influence symptoms[9]. In contrast to the numerous studies which have addressed gastro-oesophageal reflux of acid, belching or gas reflux has received little attention. In the present study a provocative test of gas reflux was developed because no standard method existed. Our requirements were that the new test should avoid mechanical

Table 1 *Variation in expired air carbon dioxide concentration*

		Expired air carbon dioxide concentration (%)	
	n	Before test (x̄(s.e.m.))	After test (x̄(s.e.m.))
Volunteers	9	2·95(0·27)	3·16(0·29)
Patients	16	3·03(0·15)	3·11(0·12)

Table 2 *Frequency of symptoms in patients*

Symptom	Patients (*n* = 16)
Postprandial fullness	11
Swelling of the abdomen	11
Urge to vomit	3
Feeling unable to vomit	3
Feeling unable to belch	6

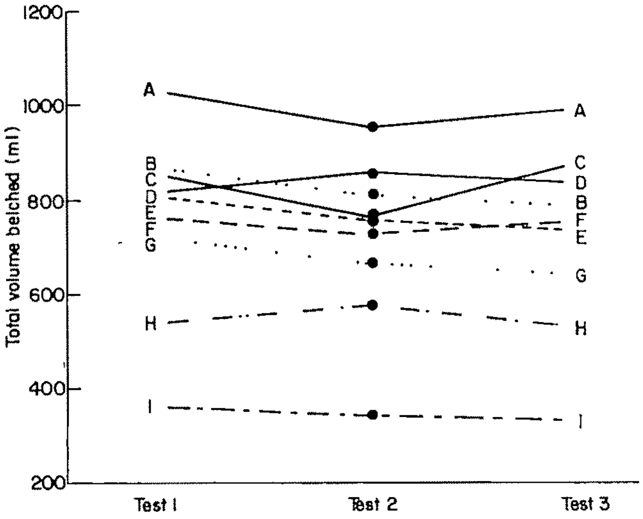

Figure 2 *Test reproducibility studies in subjects A–I. Total belched gas volumes were similar in the same individuals in all three tests. (Coefficient of intrasubject variation 4·5 per cent)*

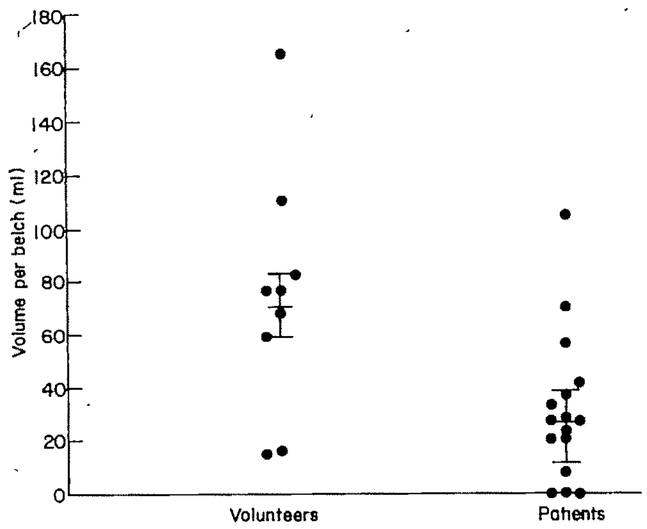

Figure 3 *Volume per belch in volunteers and patients* (P<0·02, Mann–Whitney U *test*). *Bar lines represent the median and upper and lower interquartile range*

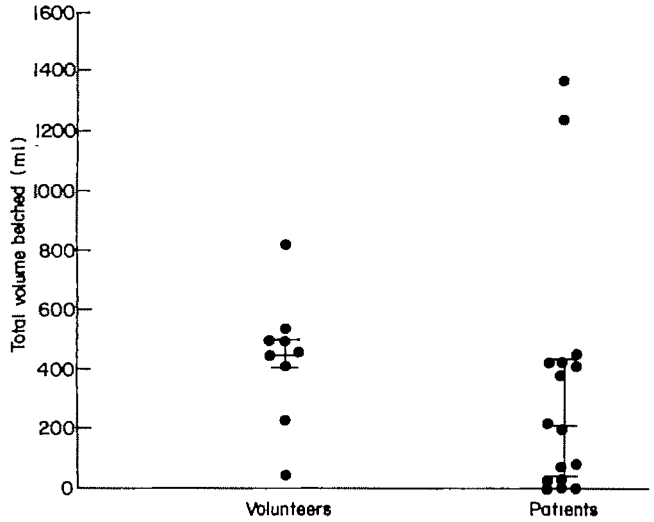

Figure 4 *Total volume belched in volunteers and patients* (P<*0·05, Mann–Whitney* U *test*). *Bar lines represent the median and upper and lower interquartile range*

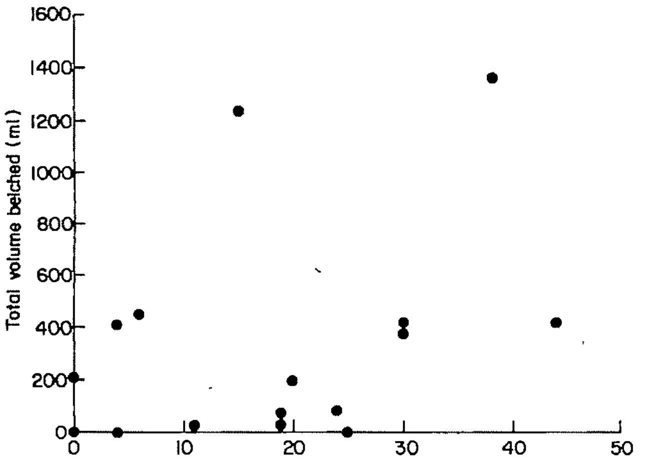

Figure 5 *Symptom scores and total belched gas volumes in patients* (*n.s. by Kendall's rank correlation*)

interference with the lower oesophageal sphincter, should allow quantification of belching, and be acceptable to patients. We therefore sought a tubeless method and induced gaseous stomach distension by oral administration of reagents which are safe in the doses used and interact with release of carbon dioxide. This gas has the advantages of a very slow rate of gastric absorption (transfer coefficient, $k=0{\cdot}0037$ ml/min per mmHg)[10] and is easily measurable by standard laboratory equipment. In this study, therefore, gastric distension was induced by 1200 ml carbon dioxide resulting from the interaction of orally administered citric acid and sodium bicarbonate. The interaction is complete in <30 s. Gastric distension by this volume is associated with minimal pressure rise[11] and caused no discomfort in our volunteers or patients.

After administration of the reagents, all subjects belched into a closed container, then filled it to capacity with expired air, in order to flush out dead space carbon dioxide. Expired air concentrations of carbon dioxide were measured before and after each experiment to take account of any small rise in breath carbon dioxide, resulting from any transmucosal diffusion of carbon dioxide, in the calculation of belched gas volumes. In the calculation of belched gas volumes, expired air concentration of carbon dioxide (C_e) was taken as the mean of these measurements, but in practice C_e change due to carbon dioxide transmucosal absorption was minimal

All belched gas was collected for 1 h after administration of the reagents. Belching frequency was maximal within the first 10 min and few belches occurred later, which is in agreement with the observations of McInally *et al.*[11]. The developed test had an acceptably low coefficient of variation (4·5 per cent) for within-subject measurements, which compares with that of diastolic blood pressure measurements[12]. This finding supports the methodology and suggests that error sources, such as gas losses through the nose or around the apparatus, are likely to be small. The test was also very acceptable to patients, which accounts for the high rate of compliance despite the lack of any therapeutic implication for the participants.

The view that belching ability may be impaired by antireflux surgery and that this impairment may be implicated in the causation of postoperative symptoms is widely held[3,4] but scientific confirmation is lacking. The present study, however, shows that antireflux surgery patients belch smaller gas volumes than normal subjects, after a standard stimulus. It may be useful to speculate on causative mechanisms.

In the present study, the ages of the patient and volunteer groups differed However, since age is unrelated to lower oesophageal sphincter pressures[13] and liquid reflux[14], and since patterns of lower oesophageal sphincter relaxation in gas and liquid reflux are identical[15], it seems unlikely that age differences would account for differences in gas reflux.

Gas within the stomach may exit via the oesophagus by way of belching or via the duodenum. In normal subjects, only small duodenal gas losses occur within a short interval of gastric distension. For example, McInally *et al.* recovered 1550 ml of 1600 ml of instilled intragastric gas in eight subjects, who did not belch during an interval of 10 min[11]. In the present study, however, this factor could be more important because antireflux surgery patients would have reduced gastric volumes as a result of their fundoplication. Hence, duodenal gas escape could be greater and lead to reduced belching

In fundoplication, the buried oesophagus acts as a one-way valve, effective against raised intragastric pressure even when studied *ex vivo*[1]. Furthermore, the belch reflex[15], which is initiated by stretch receptors in the fundus[1], could be inhibited by the mechanics of the fundal wrap. Hence the anatomical and mechanical effects of the antireflux surgery on the gastro-oesophageal junction could also lead to belching impairment.

In this study, we have also carried out an evaluation of symptoms of the 'gas bloat' type, which has included the feeling of 'being unable to belch', in both patients and volunteers. However, no association between belched gas volumes and any individual symptom, or indeed total symptom score, was found It is possible that the small patient numbers and relatively low incidence of symptoms in the study group could be responsible for the lack of association. Alternatively, it is possible that other factors, such as alteration in gastric emptying, could contribute to some of the dyspeptic symptoms experienced by patients after antireflux surgery[16]. This study has shown that the phenomenon of belching can be quantified, but further work is required to ascertain whether the developed test is of clinical value in a diagnostic or therapeutic context

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Paper accepted 16 August 1990

Announcement

The British Journal of Surgery Society
EUROPEAN FELLOWSHIPS 1991

The Council of the British Journal of Surgery Society is offering up to three European Fellowships to be taken up during 1991. Fellowships are designed:

1) to allow a British surgeon to visit a surgical centre or centres of his/her choice within Europe for a period of 4–6 weeks.

2) to allow a surgeon working in another European country to visit surgical centres in Britain.

Up to £3000 is available for each Fellowship. Applicants should be between 30 and 40 years of age and should be working in surgical practice (either clinical or research) in Europe. Applicants should submit details of their proposed itinerary and its anticipated cost, together with a curriculum vitae and two letters of support from senior colleagues. They should explain briefly how such a visit might broaden their experience and assist their career. Applications should be sent to the Company Secretary, Professor R. C N. Williamson, Department of Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, DuCane Road, London W12 0NN, UK by 28 February 1991.

Br. J. Surg. 1991, Vol. 78, January, 36–40

Evaluation of the results of oesophagectomy for oesophageal cancer

The long-term results of standard techniques of oesophagectomy were examined in 127 patients with squamous cell carcinoma of the oesophagus. A near-total oesophagectomy with a cervical anastomosis was performed in 93 patients and an oesophagogastrectomy with an intrathoracic anastomosis was carried out in 34 patients. One hundred and eight patients had a curative oesophagectomy and 19 patients had a palliative resection. Eighty patients received radiotherapy to the tumour bed. There were 15 deaths in hospital and the overall 5-year survival rate including perioperative deaths was 13·2 per cent. Survival was adversely affected by incomplete excision of macroscopic tumour ($P<0{\cdot}001$), *positive regional lymph nodes* ($P<0{\cdot}05$) *and distant lymphatic metastases* ($P<0{\cdot}02$). *The 5-year survival rate of patients with tumour invasion beyond the oesophageal wall* (T_3) *and negative nodes was 20 per cent. Postoperative irradiation had no effect on the survival of patients with gross residual tumour. Complete clearance of microscopic tumour was achieved in 50 per cent of patients with* T_3 *tumours and this group did not benefit from adjuvant radiotherapy. Survival in patients undergoing curative oesophagectomy with residual microscopic tumour, however, was significantly improved by irradiation of the tumour bed* ($P<0{\cdot}01$). *These results suggest that the survival of patients can be increased significantly by the excision of all gross tumour and by identification of those who will benefit from local radiotherapy.*

A. Mannell and
P. J. Becker*

Department of Surgery, University of the Witwatersrand and
**Department of Biostatistics of the Medical Research Council (Transvaal Branch), Johannesburg, South Africa*

Correspondence to:
Professor A. Mannell, Department of Surgery, Medical School, York Road, Parktown, 2193
Johannesburg, South Africa

Resection of oesophageal cancer offers the best result in terms of palliation or cure and the proximal and distal lines of excision should be as distant from the tumour as possible to reduce the risk of anastomotic recurrence[3]. The lateral extent of resection is a controversial issue. The biological nature of the tumour and its stage at the time of operation, rather than the extent of resection, may determine survival[2]. In blunt oesophagectomy, in which the malignant oesophagus is mobilized blindly, the possibility exists that macroscopic tumour and involved regional lymph nodes may be left *in situ*. Alternatively, survival may be influenced by the extent of lateral resection. Proponents of this view[1] excise, *en bloc*, the oesophagus, all lymphatic tissue, the thoracic duct, pericardium, pleura and non-vital intrathoracic vessels within the field of dissection extending 10 cm above and below the tumour.

The value of established techniques of oesophagectomy must therefore be questioned. Is a thoracotomy for oesophagectomy without *en bloc* resection both insufficient for cure and unnecessary for long-term palliation?

The role of adjuvant radiotherapy is unclear. The results of preoperative irradiation are conflicting[4,5] and, although encouraging results for surgery followed by irradiation have been reported[6], the results from randomized trials of postoperative radiotherapy are not published.

To provide further information in these controversial areas, the long-term results in 127 patients undergoing oesophagectomy for squamous oesophageal cancer are presented. Particular attention has been paid to the lateral margins of resection, the histopathological findings and to possible survival advantage associated with postoperative radiotherapy.

Patients and methods

Data were gathered prospectively from 127 patients undergoing oesophagectomy for squamous cell carcinoma of the thoracoabdominal oesophagus at Baragwanath Hospital, Johannesburg, from July 1978 to August 1989. Those with adenocarcinoma of the oesophagus, cancer of the cardia, gastric cancer involving the distal oesophagus and hypopharyngeal malignancy extending into the cervical oesophagus were excluded. There were 95 men and 32 women aged 23–79 years (mean 51 years). Patients underwent a barium swallow, chest radiography, indirect laryngoscopy, abdominal ultrasonography, bronchoscopy, oesophagoscopy and biopsy before operation

Computed axial tomography, radionuclide liver scans and fine needle aspiration cytology of palpable neck nodes were performed when indicated. Patients assessed as stage 1 and 2 disease using the tumour node metastasis (TNM) classification of malignant tumours[7] were selected for oesophagectomy. There was no clinical, endoscopic or radiological evidence of local extra-oesophageal spread or distant metastases, the tumour was not more than 10 cm in length and each patient was assessed as fit for thoracotomy.

A near-total oesophagectomy with a cervical oesohagogastric anastomosis (laparotomy, right thoracotomy. right neck dissection)[8] was performed in 93 cases. Thirty-four patients underwent oesophagogastrectomy of the Ivor Lewis type (laparotomy, right thoracotomy) with an intrathoracic anastomosis[8]

Tumours were resected, where possible, with a 10 cm length of proximal margin of macroscopically normal oesophagus The distal line of excision was at least 5 cm below palpable tumour. The resected specimen included regional lymph nodes, parietal pleura overlying the cancer and a cuff of diaphragm when the tumour extended to the oesophageal hiatus The vena azygos and thoracic duct were excised if these were adherent to the tumour. Distant lymph nodes were removed when evident Where all macroscopic tumour was excised, the oesophagectomy was described as 'curative'; a 'palliative' oesophagectomy denoted incomplete excision of cancer. On histological examination of the resected specimen particular attention was paid to the length of macroscopic tumour, depth of transmural invasion, the proximal and distal lines of excision, the lateral margins of resection and the lymph nodes. In each patient the tumour bed was defined by application of clips at operation to facilitate radiotherapy after

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operation This was given in daily fractions of 150–200 rad to a total dose of 4500–5000 rad.

Analyses of data

Significance analyses were performed using χ^2 tests to compare the following variables length of tumour, pathological invasion and metastases to regional and distant lymph nodes. Survival rates were estimated using the method of Kaplan and Meier[9] and the significance of clinicopathological features, including presence of residual macroscopic or microscopic tumour and postoperative irradiation, was determined using a generalized Wilcoxon test[10].

Results

Clinicopathological features

One hundred and eight patients underwent a curative oesophagectomy and 19 patients had a palliative resection. There were 15 deaths in hospital (hospital mortality rate 11·8 per cent) Tumours varied from 3 to 11 cm in length (mean 6 cm). There were two cases of cancer confined to the mucosa and submucosa (T$_2$), in 30 cases the muscularis propia was invaded (T$_2$) and 89 patients had invasion beyond the oesophageal wall (T$_3$), the depth of transmural invasion was not recorded in six cases. The status of regional lymph nodes was documented in 115 patients and distant lymph nodes in 105 patients Regional lymph nodes were involved in 41 per cent and distant lymph nodes in 32 per cent of cases. Data were available to stage 103 cases accurately using the postoperative TNM classification[7]: stage 1, two cases; stage 2, 19 cases; stage 3, 48 cases, stage 4, 34 cases. In this series, tumour length (*Table 1*) had no significant influence on depth of invasion or lymphatic metastases. There was a statistically significant association between depth of invasion (*Table 1*), regional lymph node involvement ($P<0·05$) and distant nodal metastases ($P<0·02$).

There were seven cases with microscopic involvement of the proximal line of excision: in three patients, one of whom had cancer in the upper thoracic oesophagus, resection of a 10 cm length of margin of macroscopically normal oesophagus was not achieved and three patients had severe dysplasia with carcinoma *in situ* at the proximal line of excision. In the remaining case, although the mucosa at the proximal resection margin was normal, there was a focus of invasive cancer in the adventitia The distal line of excision was involved by cancer in two patients, both undergoing near-total oesophagectomy for midthoracic tumours One of these had satellite nodules above and below the primary site and the other had a single focus of cancer limited to the mucosa at the distal resection margin. A detailed examination of the outer free surface of the resected specimen was recorded in 121 cases. In 70 patients with T$_3$ tumours who had a curative oesophagectomy, the lateral resection margins were clear of cancer in 35 but involved by microscopic tumour in the other 35 cases.

Radiotherapy

All cases were scheduled for irradiation after operation but 12 patients who had a curative oesophagectomy and three undergoing palliative resection died in hospital. Of the 112 survivors, 80 were irradiated, 30 failed to return for radiotherapy and two were not considered well enough to complete the course *Table 2* details the extent of resection and stage of disease in patients who received tumour bed irradiation and those who did not.

Table 1 *Tumour staging, length and nodal status*

Tumour (T)	Mean length (cm)	Number with positive nodes	
		Regional	Distant
T$_1$	3	0/2	0/2
T$_2$	6	7/30	5/28
T$_3$	6·5	39/81	28/72

Table 2 *Radiotherapy, extent of resection and stage of disease*

No of patients*	Radiotherapy ($n=80$)	No radiotherapy ($n=32$)
Palliative resection	9	7†
Curative resection		
Stage 1	1	1
Stage 2	14	2
Stage 3	32	8
Stage 4	14	7
Staging incomplete	10	7
Total	71	25

* Excludes hospital deaths, † includes two patients not fit for radiotherapy

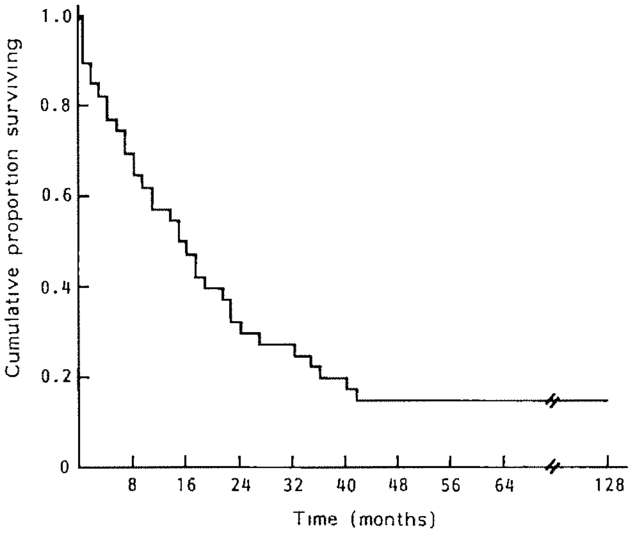

Figure 1 *Survival in 126 cases of oesophageal cancer, hospital deaths are included*

Survival (Figure 1)

One patient, for whom the date of discharge was not recorded, was lost to follow-up and has been excluded from the analysis of survival Of the remaining 126 cases, the 1-year survival rate in this series was 56 per cent; 31 per cent survived for 2 years, 22 per cent survived for 3 years, and the 5-year survival rate was 13·2 per cent (mean survival period 30 months) In patients with T$_1$, T$_2$ and T$_3$ tumours, the mean length of survival was 69, 32 and 26 months respectively. Survival was adversely affected by regional (*Figure 2*) and distant (*Figure 3*) lymph node metastases. In 22 patients with T$_3$ tumours without nodal metastases or gross residual tumour, the mean length of survival following irradiation was 45 months and the 5-year survival rate was 20 per cent (*Figure 4*)

The type of operation had no significant influence on either hospital mortality rate or length of survival: of those discharged from hospital, the mean(s.e.m) survival time was 33(6) months for patients who had a near-total oesophagectomy and 26(9) months in those undergoing oesophagectomy ($P>0·05$).

The influence of postoperative irradiation was examined in patients discharged from hospital (*Table 2*) and varied according to the extent of resection, stage of disease and histological involvement of the lateral margins of resection After palliative oesophagectomy, the mean(s.e.m.) survival time was 5(2) months for surgery alone and 12(5) months if the sites of residual tumour were irradiated, a difference which failed to reach statistical significance ($P>0·01$). The excision of all gross

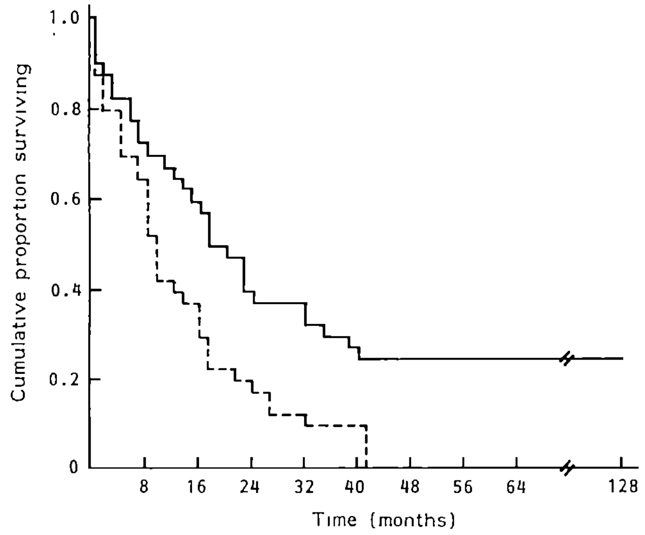

Figure 2 *Survival according to regional nodal status,* (—), *node negative* (n=*68*), *mean survival time 42 months,* (---), *node positive* (n=*46*), *mean survival time 12 months* ($P<0\cdot05$)

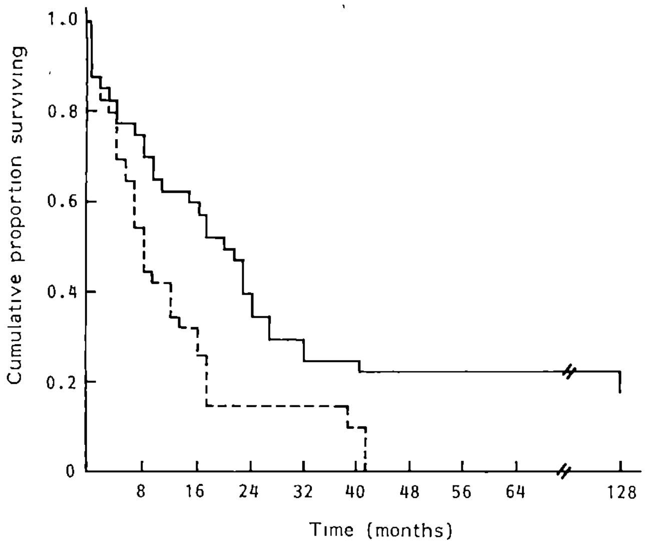

Figure 3 *Survival according to distant nodal status,* (—), *node negative* (n=*70*), *mean survival time 38 months,* (---), *node positive* (n=*34*), *mean survival time 14 months* ($P<0\cdot02$)

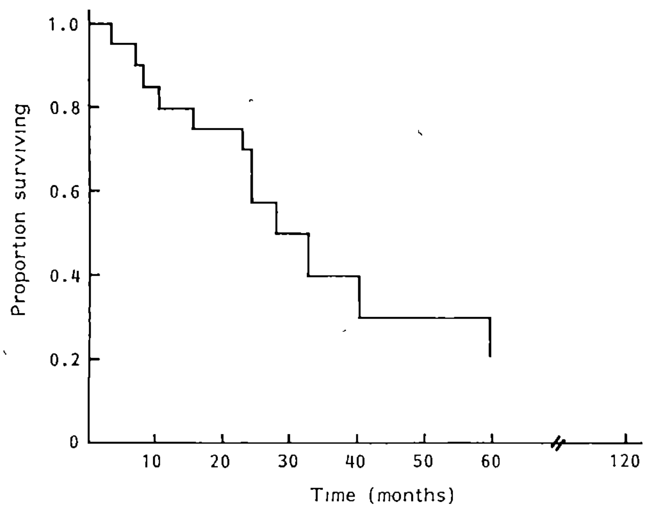

Figure 4 *Survival of patients with* T_3N_0 *tumours*

tumour tissue had a highly significant influence on survival. following curative oesophagectomy and irradiation of the tumour bed, the mean(s.e.m.) survival time was 37(6) months (*Figure 5*, $P<0\cdot001$).

Patients undergoing curative oesophagectomy included all stages of disease (*Table 2*) Given the limited number of cases with stage 1 and 2 cancer, it was not possible to examine the influence of postoperative radiotherapy in these patients. The mean(s.e.m.) survival time of patients with stage 3 disease was 38(9) months following tumour bed irradiation compared with 16(6) months for surgery alone ($P<0\cdot05$) Postoperative irradiation appeared to have a significant influence on survival of stage 4 cases: with radiotherapy, the mean(s.e.m.) survival time was 20(5) months compared with 7(2) months for surgery alone.

The survival of all patients, irrespective of stage, undergoing curative oesophagectomy was then examined with respect to the presence or absence of microscopic involvement of the lateral margins of resection. Postoperative radiation therapy had no effect on survival when the outer free surface of the resected specimen was clear of tumour: the mean survival time in these cases without radiotherapy was 37 months. However, radiation therapy had a significant effect on survival in patients undergoing curative oesophagectomy where the lateral margins of the resected specimen were microscopically involved (*Figure 6*). the mean survival in these cases for surgery alone was 13 months compared with 35 months for those who received adjuvant radiotherapy ($P<0\cdot01$).

Discussion

In other series[11,12] tumour length correlates with depth of invasion and incidence of lymph node metastases This association may have been obscured in the current study because patients with long tumours (> 10 cm) and/or evidence of extraoesophageal spread were not considered as candidates for oesophagectomy and there were only 16 cases where the tumour was less than 5 cm in length. The well documented effect[11] of the extent of transmural spread on the frequency of nodal metastases was confirmed in this series (*Table 1*).

The proximal line of excision was involved by microscopic tumour in 6 per cent of cases, which compares favourably with other reported series[13,14]. This may have been reduced to 3 per cent if the proximal margin of macroscopically normal oesophagus had been 10 cm in all patients, and confirms an earlier observation by Miller[15] that microscopic involvement occurs in only 3 per cent of cases with a proximal margin of

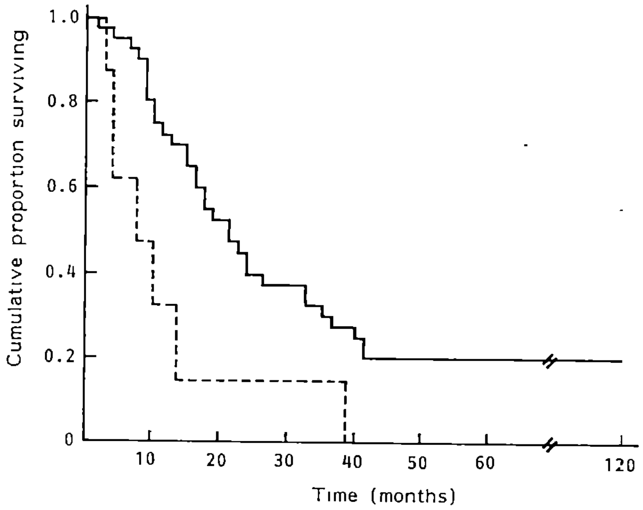

Figure 5 *Survival after 'palliative' oesophagectomy and radiotherapy* (---) (n=*9*, *mean survival time 12 months*) versus *'curative' oesophagectomy and radiotherapy* (—) (n=*71*, *mean survival time 38 months*) ($P<0\cdot001$)

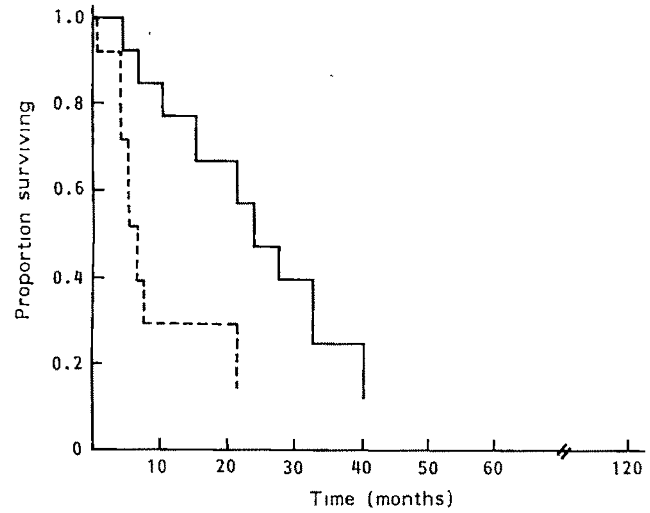

Figure 6 *Survival in patients with residual microscopic tumour;* (——), *with radiotherapy* ($n = 16$, *mean survival time 35 months*); (– – –) *without radiotherapy* ($n = 12$, *mean survival time 13 months*) ($P < 0{\cdot}01$)

10·5 cm. The distal line of excision was clear of tumour in all cases undergoing oesophagogastrectomy where sufficient stomach was resected to provide a clearance of 5 cm below macroscopic tumour. In the normal stomach it is possible to identify points of transection on the mobilized, straightened lesser and greater curvatures 10 cm distal to the cardio-oesophageal junction without compromising performance of an oesophagogastric anastomosis at the level of the clavicle[1]. Increasing the margin of distal resection to 10 cm below the tumour in every case would have benefited fewer than 2 per cent of patients in this study and does not provide a strong case for the more radical resection of the stomach practised in the *en bloc* technique[1]

In the standard techniques of oesophagectomy, a thoracotomy is performed and the oesophageal malignancy is dissected under vision. It was gratifying to find that in those cases with T_3 tumours where the outer free surface of the resected specimen was submitted to careful histological examination, complete clearance was achieved in 50 per cent. Perioesophageal tissue is not removed when blunt oesophagectomy without thoracotomy is performed for intrathoracic oesophageal cancers and it is highly unlikely that total excision of a T_3 tumour is possible with the latter technique.

Adenocarcinomas of the oesophagus and cardia are less radiosensitive and have a poorer prognosis than squamous tumours[16]. They commonly arise in the distal oesophagus and are frequently resected using an Ivor Lewis approach[17]. All adenocarcinomas were excluded from this review and the type of operation did not therefore influence survival.

In the absence of a prospective, randomized trial of postoperative radiotherapy, the findings in this series cannot be regarded as conclusive but an attempt has been made to compare survival, with and without tumour bed irradiation, in cases of similar stage and extent of resection.

Analysis of survival in patients who had a palliative oesophagectomy emphasizes the importance of complete excision of all macroscopic tumour. Seventeen of the 19 palliative oesophagectomies were performed in the first 4 years of this study and, with experience, curative oesophagectomy should be possible in all except T_4 cancers invading vital structures. Radiotherapy failed to improve survival and little or no survival advantage is gained by simply 'debulking' tumour. Langer *et al.*[18] also found no survival advantage for palliative oesophagectomy and postoperative irradiation of residual tumour.

In contrast radiation therapy did confer a highly significant survival advantage on those who had a curative oesophagectomy and were found to have microscopic involvement of the lateral resection margins. The results of this study suggest that local radiotherapy is not indicated where the lateral resection margin is clear.

In this series the 5-year survival rate in patients with full-thickness wall penetration without positive lymph nodes was 20 per cent. The 5-year survival rate after *en bloc* oesophagectomy for similar cases is 15 per cent[19]. *En bloc* oesophagectomy does not appear to offer a significant survival advantage over the standard techniques of oesophagectomy combined with postoperative irradiation.

It is difficult to prove that excision of involved regional lymph nodes improves survival because a prospective randomized study of patients with and without local lymphatic metastases left *in situ* is not feasible. The results of blunt oesophagectomy for intrathoracic cancers cannot address this question as the regional lymph nodes are not removed for histological examination Clearance of all microscopic cancer, whether in the oesophagus or lymph nodes, will reduce tumour bed recurrence to less than 10 per cent[20] and 5-year survival rates of 15 per cent[6] have been reported following excision of local lymphatic metastases. Unlike transhiatal oesophagectomy, open thoracotomy enables the surgeon to define the tumour bed to allow accurate administration of local radiotherapy. In this series there were 32 patients with stage 3 disease, which includes T_3 tumours and/or involved regional nodes, who were managed by formal transthoracic resection under vision and tumour bed irradiation. The mean(s.e.m.) survival time in this subset of patients was 38(9) months. This compared favourably with mean survival times of 6·5 and 14 months following removal of intrathoracic cancers by blind dissection reported in recent literature[2,21]. Comparison of results from different centres must be interpreted with caution but the findings of the current study support the observation that survival of patients with stage 3 disease can be improved by adequate locoregional treatment of oesophageal cancer[6].

In this series no patient with evidence of disseminated disease at presentation was selected for oesophagectomy but biopsy of distant lymph nodes revealed that 34 patients had stage 4 disease of whom 26 had undergone curative resection. Follow-up of 21 of the latter (*Table 2*) showed a survival advantage for those receiving tumour bed irradiation. The prognosis in cases with distant nodal metastases is very poor but this result suggests that the period of palliation may be prolonged by local control of disease.

In conclusion, the surgeon can make a significant contribution to the survival of patients undergoing oesophagectomy for oesophageal cancer by removing all macroscopic tumour. Excision of non-vital structures adherent to intrathoracic cancers will ensure complete microscopic clearance in at least 50 per cent of tumours with invasion of the adventitia Careful histological examination of the outer free surface of the resected specimen will identify patients most likely to benefit from postoperative radiation therapy. Data from this non-randomized series supports the contention that outcome is not solely determined by stage of disease and that survival can be influenced by conduct of the operation and by adjuvant therapy. It is unlikely that the standard techniques of oesophagectomy will be superseded by more, or less, radical approaches to resection of oesophageal cancer.

Acknowledgements

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Use of vascular staplers in major hepatic resections

G. P. McEntee and D. M. Nagorney

Department of Surgery, Mayo Clinic and Foundation, 200 First Street SW, Rochester, Minnesota 55905, USA
Correspondence to. Dr D. M. Nagorney

Control of portal venous inflow and hepatic venous outflow during formal hepatic lobectomy is classically obtained by application of vascular clamps and stump ligature. The risk of slipped ligature or luminal compromise after simple ligation is high because of the short extrahepatic course and the wide diameter of these vessels. Alternatively, a running vascular suture can be used[1]. Recently, Voyles and Vogel described the use of a vascular stapler to ligate the right hepatic vein after parenchymal transection[2]. We report a broader application for the vascular stapler during major hepatic resection based on a recent experience of 80 major hepatic resections performed since 1988.

Surgical technique

Hepatic lobectomy is preceded by hilar vascular control. The right or left branch of the hepatic artery is ligated and divided. The portal venous branch which lies posterior to the ipsilateral bile duct is exposed by retracting the overlying bile duct contralaterally and mobilizing the vein. A small posteroinferior branch frequently arises from the right portal vein extrahepatically and requires separate suture ligation. Depending upon vessel size, an appropriate size vascular stapler (3M, St Paul, Minnesota, USA; PI 15 or PI 30) is guided around the right or left portal vein beneath its inferior margin (*Figure 1*). The pin is inserted and the stapler is carefully positioned to ensure that the lumen of the main portal vein at its bifurcation will not be compromised after staple firing and the entire circumference of the lobar portal vein branch will be contained within the staple line. The instrument is set and fired While the left main portal vein is always of sufficient length extrahepatically to allow clamp placement distal to the stapler with subsequent vessel transection and distal stump ligation, the right is occasionally too short and broad. In this situation, since serious retrograde haemorrhage is precluded because of previous control of arterial inflow, the vein is transected distal to the stapler without clamping The transected distal vein is grasped with forceps and suture ligated.

The right hepatic vein is exposed after completely mobilizing the right lobe, dividing the retrocaval ligament[1] and ligating the small direct veins between segments VI and VII and the inferior vena cava Further exposure of the right hepatic vein is completed by bluntly dissecting the vein from its medial mesenchymal attachments. An appropriate size vascular stapler is passed gently around the vein using a dissecting angled clamp as a guide if necessary (*Figure 2*). The stapler is carefully positioned to avoid caval compromise, set, and fired. Typically the right hepatic vein is of sufficient length to accommodate a clamp on the hepatic side of the stapler. Because vascular inflow has already been controlled, the vessel may be safely transected with minimal blood loss and the stump suture ligated.

Left hepatectomy or left posterior segmental resection requires ligation of both the middle and left hepatic veins. Typically, these two veins join within the hepatic parenchyma before entering the inferior vena cava. The confluence of the two veins is usually broad and horizontal to the axis of the inferior vena cava; extrahepatic exposure is complicated by the presence of the adjacent caudate lobe (segment I) Therefore, using the same technique, the stapler is used to close the confluence of the middle and left hepatic veins or left hepatic vein only after the parenchyma has been transected and the relevant venous anatomy is clearly defined

Discussion

We have used the vascular stapler for 80 hepatic lobectomies (right 56, left 24) Lobar portal venous branches were closed using the stapler in all cases. The right hepatic vein was stapled before parenchymal transection in 37 (66 per cent), after transection in 16 (29 per cent), and was considered unsuitable for stapling in three patients (5 per cent). The primary

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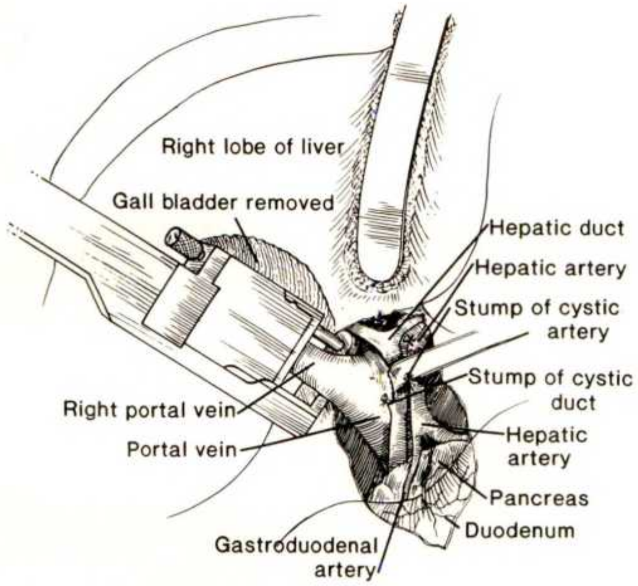

Figure 1 *Stapling the right portal vein*

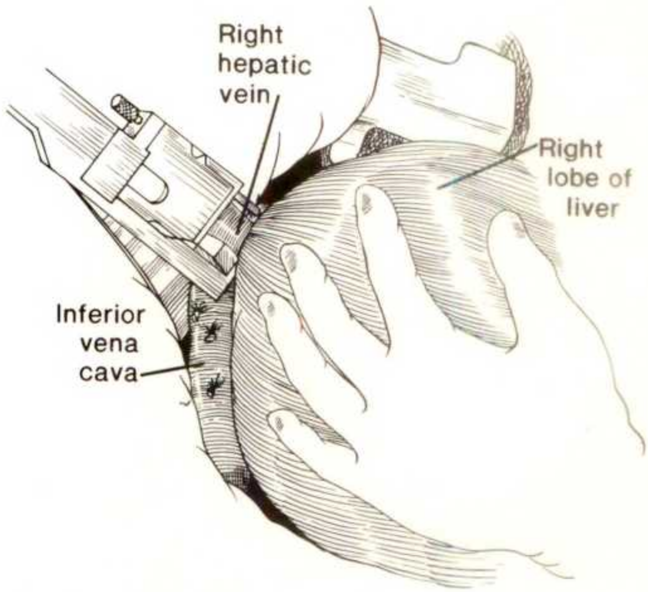

Figure 2 *Stapling the right hepatic vein*

contraindications to stapling before or after parenchymal transection were limited venous access from large adjacent tumour or a very short extrahepatic course. Of 24 left lobectomies, only two left hepatic veins (8 per cent) were considered unsuitable for staple closure following parenchymal transection. Occasionally the edge of the staple line required reinforcement with vascular sutures for minor bleeding. No major complications specifically related to the stapled veins have been encountered to date. Vascular staples were associated with insignificant imaging artifacts on follow-up computed tomograms.

We believe that the vascular stapler facilitates reliable and expedient closure of both the portal and hepatic veins. Control of both veins before parenchymal transection reduces haemorrhage associated with major hepatic resection. In those patients in whom a very short extrahepatic right or left hepatic vein prohibits safe isolation and staple ligation, we favour stapling the vein through residual hepatic parenchyma before parenchymal transection is complete as recommended by Voyles and Vogel[2].

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Prolonged intermittent clamping of the portal triad during hepatectomy

D. Elias,
E. Desruennes* and
P. Lasser

*Departments of Digestive Oncologic Surgery and *Anaesthesiology, Institute Gustave-Roussy, Villejuif, France*

Correspondence to:
Dr D. Elias, Service de Chirurgie Digestive Carcinologique, Institut Gustave-Roussy, Rue Camille-Desmoulins, 94805 Villejuif Cedex, France

From 112 consecutive hepatectomies for malignant tumours performed with intermittent portal triad clamping, we have retrospectively selected the 20 cases in which clamping exceeded 90 min. Intermittent portal clamping of prolonged duration was used because of abnormal liver texture in 13 cases (mainly patients who had received intra-arterial chemotherapy) and/or because of technically difficult hepatectomy. The mean(s.d.) duration of intermittent portal clamping was 109(18) min and in two cases it exceeded 140 min (148 and 150 min). There was no postoperative mortality and the rate of postoperative morbidity was 35 per cent. Postoperative changes in biochemical liver tests were not major and transient hepatic failure occurred in only one patient following subtotal resection of the liver. We conclude that intermittent portal clamping is a useful manoeuvre in partial hepatectomy when resection is difficult or prolonged, or when the liver parenchyma is abnormal. Such clamping may be used for longer than 120 min without major complications.

Portal triad clamping was described by Pringle[1] in 1908 as a means of reducing bleeding from the raw surface of the liver during parenchymal resection. Currently it is commonly accepted that the human liver can tolerate a period of normothermic ischaemia extending beyond 15–20 min[2,3]. More recently some studies have reported that one period of portal triad clamping could be well tolerated for a longer duration. Delva *et al.*[4] reported the use of this procedure in 107 patients undergoing hepatectomy; the mean(s.d.) duration of clamping was 30·4(1·4) min (range 8–70 min). Similar results were reported by Nagasue *et al.*[5] in 15 cirrhotic patients: the mean duration of clamping in this series was 19 min (range 2–32 min). One prolonged period of portal triad clamping is not the only way to suppress hepatic inflow, and since 1987 we have systematically used multiple intermittent clamping in the course of 112 consecutive hepatectomies for malignant tumours in order to prolong the duration of liver normothermic ischaemia and decrease blood loss during operation. Among these cases, intermittent clamping with a duration of more than 90 min was performed in 20 patients (18 per cent). The purpose of this report is to evaluate the course of these 20 patients after operation in order to determine the tolerance and benefits of such clamping.

Patients and methods

Between 1983 and May 1987 we performed 64 liver resections with one period of prolonged portal triad clamping which did not exceed 60 min (mean(s.d.) duration 42(1·2) min). In some cases of technically difficult hepatectomy, we considered that the completion of the parenchymal section was far too hurried. Accordingly, after May 1987 we decided to use intermittent portal triad clamping without limiting duration. One hundred and twelve consecutive liver resections were performed with this technique between May 1987 and November 1989. We selected retrospectively the 20 cases in which intermittent clamping for longer than 90 min was used so as to determine the reasons for prolonged clamping and assess the degree of tolerance of such protracted clamping.

Intermittent portal triad clamping was performed by snaring a loop which encircled the hepatic pedicle. Clamping was used only during section of the liver parenchyma. A simple cooking-timer was programmed for 20 min and we stopped the section as soon as it rang. Clamping was then interrupted for 5 min and the raw liver surfaces were gently compressed manually during this time. Clamping was then resumed for 20 min, and so on.

There were 11 men and nine women in whom prolonged intermittent clamping was used; their mean(s.d.) age was 53·1(10·1) years (range 35–68 years). The mean(s.d.) duration of clamping was 109(18) min (range 90–150 min). In two patients it lasted for more than 140 min (148 and 150 min). The mean(s.d.) blood loss was 2·3(1·7) litres (range 0·8–8·8 litres); it was less than 2·7 litres in all but two cases in which the loss was 3·5 and 8·8 litres respectively.

The liver parenchyma was abnormal in 13 of the 20 cases due to fibrosis following intra-arterial chemotherapy ($n = 7$), steatosis in association with obesity ($n = 4$), cirrhosis due to haemochromatosis ($n = 1$) and chronic cholestasis ($n = 1$).

The liver resections performed are shown in *Table 1*. Ten median hepatectomies (resection of segments IV, V and VIII according to Couinaud's classification[6]) were performed. In three of these cases complete dissection of the portal triad bifurcation was difficult due to the proximity of the tumour and in one case the median hepatectomy was extended to partial resection of segment II.

Blood tests were performed before operation in all patients and included complete blood count, coagulation profile with prothrombin time and partial thromboplastin time, and complete serum biochemistry screening with serum alkaline phosphatase, bilirubin, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, total protein, albumin and creatinine determinations. For these large hepatectomies, a complete study of blood count and coagulation factors was carried out at the end of the operation, and these same postoperative tests were carried out at least every day during the first week and twice per week during the following week.

Correlations between clamping duration and parameters obtained before, during and after operation were studied. Statistical analysis were carried out using the χ^2 test.

Results

No postoperative mortality occurred in the 20 patients undergoing multiple intermittent portal triad clamping.

There was no postoperative morbidity in 13 patients (mean length of hospital stay 12·4 days). There were two patients with pleural effusions, two with subphrenic abscesses, one with phlebitis and one with a wound abscess (mean length of hospital stay in these seven patients was 14·7 days). One patient had transient hepatic failure with ascites after resection of the liver except for segments II and III (length of hospital stay 37 days).

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Table 1 *Extent of resection and liver parenchymal pathology in 20 patients where duration of intermittent portal triad clamping exceeded 90 min*

		Liver parenchyma				
Extent of resection	No. of patients	Normal liver parenchyma	Fibrosis*	Lipidic steatosis	Liver cirrhosis	Chronic cholestasis
Median hepatectomy (IV–V–VIII)	9	2	4	2	1	
Median hepatectomy partially extended to II	1		1			
Right hepatectomy extended to IV and I	1					1
Right hepatectomy + one left wedge resection	2		2			
Right hepatectomy	1			1		
Left hepatectomy + right wedge resection (× 4)	1	1				
Left hepatectomy + segmentectomy V	1	1				
Segmentectomy VIII + bisegmentectomy II–III	1	1				
Bisegmentectomy VI–VII + segmentectomy IV	1	1				
Large wedge resections (× 4)	1	1				
Large wedge resections (× 5)	1			1		
Total	20	7	7	4	1	1

* Fibrosis following intra-arterial chemotherapy

Table 2 *Changes in serum biochemical and haematological parameters following partial hepatectomy where intermittent portal triad clamping exceeded 90 min*

	Day −1	Day 1	Day 2	Day 3	Day 7	Day 10
Serum glutamic oxaloacetic transaminase (units/l)	26(12)	555(408)	407(315)	120(104)	59(50)	45(32)
Serum glutamic pyruvic transaminase (units/l)	37(23)	489(421)	578(345)	337(455)	150(84)	122(94)
Alkaline phosphatase (units/l)	129(73)	86(32)	117(71)	145(80)	226(140)	226(146)
Bilirubin (μmol/l)	11(13)	30(13)	29(21)	35(33)	17(7)	16(8)
Prothrombin time (%)*	102(19)	73(12)	79(14)	89(21)	94(15)	90(14)
Factor II (%)*	109(34)	53(18)	67(9)	72(16)	64(17)	79(21)
Factor V (%)*	102(28)	58(25)	65(17)	76(29)	94(26)	104(30)

Values are mean(s.d.); * percentage of control

Postoperative changes in biochemical liver tests are presented in *Table 2*: no crucial changes occurred in spite of prolonged clamping.

With regard to the parameters obtained before operation in this group of 20 patients, the duration of clamping was correlated with the percentage of liver involvement ($P = 0{\cdot}09$) but not with presence of pathological parenchyma, age or biochemical disorders (*Table 3*).

During operation there was a significant correlation between duration of clamping and blood loss ($P = 0{\cdot}001$) (*Table 3*).

After operation no significant correlation was found between duration of clamping and postoperative biochemical upset or duration of hospitalization (*Table 3*).

Discussion

The retrospective study of these 20 cases in which intermittent portal triad clamping of more than 90 min duration (mean 109 min) was used showed no postoperative mortality and an acceptable morbidity rate of 35 per cent. There were no major modifications in biochemical or haematological parameters after operation.

It is important to note that intermittent clamping was used in patients with abnormal liver parenchyma in 65 per cent of the cases. The absence of major postoperative disturbances in liver function in these 20 cases seems to indicate that the duration of clamping can be prolonged beyond 90 min without complications. The two cases where the duration exceeded 140 min, in whom respectively 30 and 40 per cent of functional liver parenchyma remained, support this contention.

Table 3 *Relationships between duration of intermittent clamping of the portal triad for more than 90 min and parameters observed before, during and after operation*

	r	*P*
Before operation		
Tumour involvement	0·42	0·09
Age	0·15	0·56
Pathological parenchyma	−0·35	0·17
Serum bilirubin	−0·17	0·52
Serum alkaline phosphatase	0·29	0·25
Serum γ-globulin	0·22	0·39
SGOT	−0·17	0·51
SGPT	−0·03	0·89
Prothrombin time	0·20	0·44
During operation		
Blood loss	0·70	0·001*
After operation†		
Hospital stay	−0·006	0·98
Serum bilirubin (day 3)	0·23	0·35
Serum alkaline phosphatase‡	–	–
Serum γ-globulin (day 7)	0·21	0·37
SGOT (day 2)	0·33	0·20
SGPT (day 3)	0·004	0·99
Prothrombin time (day 1)	0·48	0·30

SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; * only this *P* value reached significance; † for parameters after operation, only the maximal value was considered and the day of the maximal value is reported; ‡ no study feasible: the continuous increase after operation reflects liver regeneration

The indications for intermittent clamping were not selective. We have used this procedure systematically and the arbitrary limit of 90 min was exceeded in 18 per cent of our cases. Prolonged clamping was used when liver resection was performed on abnormal parenchyma and when raw surfaces or skeletonization of second or third order portal branches was effected. In our experience, the most difficult liver texture to work with is the parenchyma following intra-arterial chemotherapy. At crushing section the tissue is very soft and without consistency. Careful, millimetre by millimetre progression is mandatory with clipping of every thin vascular or biliary structure. In spite of this extreme caution, tears occur frequently in these structures and necessitate needle suture. The flabbiness of these tissues is very different from the rigidity of cirrhotic parenchyma. Histologically the changes correspond to sclerosing cholangitis with central vein lesions (dilatation and fibrosis) and moderate hepatocellular necrosis or cholestasis in the centrolobular area[7]. Only one of our 20 patients had a cirrhotic liver, mainly because large resections are not usual for hepatocellular carcinoma in association with cirrhosis.

The other reason for prolonged liver section was large raw surfaces of parenchyma. The main cause of this problem was median (or central) hepatectomy; in our experience primary dissection of the right portal branch bifurcation is required with ligature of the anterosuperior trunk feeding segments V and VIII. The passage along the left side of the right hepatic vein is very long and leaves the largest raw surface; resection of segment IV is easier. In our data involving 176 hepatic resections for malignant tumours, only ten median hepatectomies have been performed and all of them required at least 90 min of intermittent portal clamping. They represent half of the 20 cases in this series. All the other resections left large raw surfaces except in the two cases of right hepatectomy, but in these two cases resection was undertaken through parenchyma following chemotherapy.

The main advantage of intermittent clamping is that it reduces blood loss during operation. Mean blood loss was 2·3 litres in these 20 difficult hepatectomies and blood loss was always less than 2·7 litres except in two cases. The first of these two cases lost 8·8 litres during right hepatectomy with two large metastasectomies from within the left liver for multiple carcinoid metastases. Such livers with carcinoid metastases are usually hypervascular, and in this case the patient had a definitive embolization of the right portal branch in order to induce hypertrophy of the left liver 1 month before hepatectomy[8]. The second patient lost 3·5 litres of blood during a median hepatectomy. This patient had received intra-arterial hepatic chemotherapy with tetrahydro-piranyl-Adriamycin® (Roger Bellon, Neuilly, France) (70 mg every 3 weeks for six courses) and had undergone two wedge resections of the right liver for metastases 10 months before. Reduction in blood loss during operation is directly related to a decline in postoperative mortality and morbidity rates in that there is a close relationship between the amounts of blood lost and replaced and the rate of perioperative complications in major liver surgery[4,9–13]. The frequency of liver failure following hepatectomy is also related to blood loss during operation[4,8] and not to the duration of liver ischaemia[4,12]. Because blood loss during operation is a decisive factor in early prognosis following liver resection, clamping which permits reduction in bleeding is in our view an indispensible manoeuvre. In cases of difficult, extensive hepatectomy it is vital to know whether prolonged clamping can be employed without great risk. The use of intermittent clamping for a mean duration of 109 min in this series, without any severe complications after operation, shows that this method can be extensively employed. It avoids haste and allows time to complete local haemostasis and to repair biliary injury. In some cases it permits resection of tumours usually considered to be unresectable.

It is probable that intermittent portal triad clamping can be well tolerated for more than 120 min by the human liver during hepatic resection.

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Detection of colorectal liver metastases using intraoperative ultrasonography

R. M. Charnley,
D. L. Morris,
A. R. Dennison,
S. S. Amar* and
J. D. Hardcastle

Departments of Surgery and
**Radiology, University of*
Nottingham, Queen's Medical
Centre, Nottingham, UK
Correspondence to:
Mr R. M. Charnley, Department of
Surgery, West Block, University
Hospital, Nottingham NG7 2UH, UK

Intraoperative ultrasonography of the liver has been carried out in 99 patients undergoing surgery for colorectal cancer. Palpation of the liver, preoperative abdominal ultrasonography and computed tomography scanning were also performed in all patients. Metastases were identified in 26 of the 99 patients (26 per cent). Intraoperative ultrasonography diagnosed more metastases than palpation, abdominal ultrasonography or CT scanning, identifying metastases in 24 of the 26 patients, including six patients in whom the metastases were not detected by any other technique. Identification and localization of impalpable liver metastases is therefore possible using intraoperative ultrasonography.

Keywords: Intraoperative ultrasonography, colorectal cancer, occult hepatic metastases

More then 20 per cent of patients with colorectal cancer have occult liver metastases present at the time of their initial operation[1,2]. These metastases are impalpable at operation because they are too small to feel, because they exist in a part of the liver that is difficult to palpate or, occasionally, because they exist in a liver surrounded by adhesions. Contact ultrasonography of the liver, performed at post-mortem examination, has the ability to detect liver metastases down to a diameter of 5 mm^3. Intraoperative ultrasonography should therefore be able to detect a proportion of liver metastases which are present but impalpable at operation. Apart from increasing the yield of metastases detected overall, the technique might identify more patients with resectable metastases.

Patients and methods

Familiarization with the ultrasonographic anatomy of the liver was obtained by reference to standard texts[4,5] and a study which involved scanning livers at post-mortem examination. This has been described previously[6]. One hundred patients with colorectal cancer were identified as being suitable for intraoperative hepatic ultrasonography. In one patient extensive intraperitoneal adhesions following previous surgery made examination of the liver by palpation and by intraoperative ultrasonography impossible. Identification of normal structures and pathological lesions within the liver was carried out by intraoperative ultrasonography in 99 patients who also underwent liver palpation at laparotomy, preoperative abdominal ultrasonography and computed tomography (CT) scanning of the liver. Eighty-seven patients had primary colorectal cancer and 12 patients were undergoing surgery for recurrent disease (either local recurrence or metachronous liver metastases). Of the patients with a primary carcinoma 14 were classified as Dukes' A, 24 were Dukes' B, 33 were Dukes' C and 15 had overt liver (13 patients) or lung (2 patients) metastases (referred to as Dukes' 'D'). One patient's primary carcinoma was unresectable. Sixty-seven patients with primary carcinoma had an apparently curative resection of their disease.

Intraoperative ultrasonography was peformed using a Bruel and Kjaer (Naerum, Denmark) ultrasound scanner 1846 and intraoperative ultrasound probe 8537. The probe (incorporating a 7 MHz transducer at its tip) is finger shaped, is easily held in one hand over the surface of the liver and produces a sector scan of the liver substance. It can be easily applied to all palpable parts of the liver surface even through a lower midline incision.

After bimanual palpation of the liver the intraoperative ultrasound scan was commenced at the right posterior aspect of the right lobe. The probe was passed in a horizontal direction back and forth across each lobe until the whole of the anterior surface had been scanned, the image appearing as a sagittal scan of the liver substance on a nearby screen. The examination was performed in the same way with the probe on the undersurface of the liver so that all of the liver substance was imaged. To enhance imaging of the surface of the liver, a water-filled balloon may be attached to the tip of the probe. The first 40 examinations performed were timed, the median time being 11 min. The images produced were recorded on to videocassette and hard copies of these images were transferred onto X-ray film when necessary. The results of liver palpation and of intraoperative ultrasonography were recorded in detail separately and the images were reviewed at a later date by one of us (R.M.C.). Lesions were reported as being metastases if there was histological proof, if there was evidence of subsequent enlargement on serial scanning or if the lesions demonstrated the characteristic ultrasonographic appearance of metastases. At the time of the intraoperative ultrasound examination, the results of the other investigations (including the surgeon's palpation of the liver) were not available to the intraoperative ultrasonographer.

Preoperative abdominal ultrasonography of the liver was performed in all patients using a Phillips Sonodiagnost (Philips Medical Systems, London, UK) ultrasound machine (3·5 MHz). The liver was routinely examined in transverse and sagittal sections. CT scanning of the liver was performed in all patients using a Picker International (IGE Medical Systems Ltd., Slough, UK) fourth generation CT scanner taking 10 mm slices at 15 mm intervals with intravenous contrast enhancement. The radiologists reporting these techniques did not have available the findings of palpation or intraoperative ultrasonography. The number of lesions detected (up to ten) was recorded. The position of all lesions detected by palpation, intraoperative ultrasonography and CT scanning was also recorded (this was not possible for abdominal ultrasonography).

In the design of this study the recommendations of Freedman concerning the design of imaging studies[7] have been taken into account. In particular, the imaging techniques have been performed and reported as part of the routine hospital service environment with the CT scanning being carried out by a consultant radiologist and preoperative ultrasonography by consultants and senior registrars in radiology.

The patients in this study are being carefully followed by serial carcinoembryonic antigen measurements and CT scanning at 2 years. In addition, imaging is carried out at any time if clinically indicated.

Results

Three patients had benign hepatic lesions identified. Two patients had simple hepatic cysts, confirmed at surgery, and another patient had equivocal lesions on CT scan which at operation were palpated and imaged by intraoperative ultrasonography. They had the appearance of haemangiomata and this was confirmed by histology.

In total 26 of the 99 patients (26 per cent) had metastases detected at the time of surgery by one or more of the investigations. The number of metastases identified by each technique in these patients is shown in *Table 1*. Metastases were identified by palpation in 18 patients, by abdominal ultrasonography in nine patients, by CT scan in 18 patients and by intraoperative ultrasonography in 24 patients. The 18 patients with metastases identified by palpation comprised the 13 patients with Dukes' 'D' primary carcinoma and five

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Table 1 *Number of metastases detected by each technique*

Patient no.	Dukes' classification	Palpation	Abdominal ultrasonography	Computed tomography	Intraoperative ultrasonography	Diagnosis confirmed
1	Recurrence	2	2	2	8	Yes
2	Recurrence	0	0	0	1	No
3	Recurrence	>10	>10	>10	>10	Yes
4	'D'	1	0	0	1	Yes
5	'D'	>10	>10	>10	>10	Yes
6	'D'	6	0	3	4	Yes
7	Recurrence	1	1	1	1	Yes
8	C	0	0	0	1	No
9	A	0	0	2	0	No
10	'D'	>10	>10	>10	>10	Yes
11	'D'	3	0	2	3	Yes
12	'D'	1	0	1	1	Yes
13	'D'	7	>10	>10	>10	Yes
14	'D'	4	0	1	>10	Yes
15	Recurrence	7	0	2	9	Yes
16	B	0	0	0	1	Yes
17	'D'	>10	0	0	>10	Yes
18	C	0	0	0	1	Yes
19	C	0	0	1	0	Yes
20	'D'	3	6	7	7	Yes
21	C	0	0	0	1	Yes
21	'D'	2	0	2	2	Yes
23	'D'	1	1	1	1	Yes
24	A	0	0	0	1	No
25	Recurrence	1	1	1	1	Yes
26	'D'	>10	0	9	>10	Yes

patients with recurrent carcinoma. There were six patients in whom metastases were detected by intraoperative ultrasonography although palpation, abdominal ultrasonography and CT scan were normal. Proof of metastatic disease by histology or by serial scanning has so far been possible in 22 out of 26 patients with metastases and in three out of six patients in whom occult metastases were identified solely by intraoperative ultrasonography. Intraoperative ultrasonography also demonstrated additional impalpable lesions in nine of the 18 patients (50 per cent) in whom palpable lesions were present including four of the patients with more than ten metastases found on palpation and patient 11 who had a palpable lesion missed by intraoperative ultrasonography and an impalpable lesion found by intraoperative ultrasonography, having four metastases in total.

Intraoperative ultrasonography identified impalpable metastases which were hyperechoic (brighter than the surrounding liver substance), isoechoic (of the same brightness as the surrounding liver substance) or hypoechoic (darker than the liver substance) (*Figure 1*). Intraoperative ultrasonography proved to be very useful for detecting metastases deep within the liver but was not so good for imaging small surface lesions, although these surface lesions were easily palpable. The smallest impalpable lesion detected by intraoperative ultrasonography was 5 mm in diameter (*Figure 1c*).

The impalpable metastases which were identified by intraoperative ultrasonography were most commonly in the right lobe or in segment 4. In the six patients who had impalpable metastases identified solely by intraoperative ultrasonography, the lesions were in segments 3, 4, 4, 5, 7 and 7 respectively.

Discussion

Intraoperative ultrasonography detected occult lesions in 6 per cent of patients undergoing surgery for colorectal cancer or in five out of 67 (7 per cent) patients undergoing curative surgery for primary colorectal cancer. The follow-up period is currently too short to comment on the presence or absence of overt metastases in these patients. False negative and positive scans will be better determined after the 5-year follow-up period. Other modalities, particularly CT scanning, have previously been shown to produce a high rate of false positive results[1].

A possible reason for the lower detection rate of occult lesions in these 99 patients may be due to patient selection. All patients were operated on in routine lists. The number of occult metastases is probably greater in patients operated on as an emergency, because a less thorough examination of the liver is made under these conditions. The high incidence of patients with Dukes' A carcinomas (16 per cent) in this study is a reflection of the earlier stage cancers detected by the Nottingham Colorectal Cancer Screening Project[8].

Patients with rectal and colonic cancer, who had lower abdominal (36 per cent) and 'long' abdominal (64 per cent) incisions, were included. The position of the incision did not influence detection of metastases: 24 per cent of patients with long incisions and 30 per cent of patients with lower incisions had metastases identified.

Detected small impalpable lesions may not be amenable to biopsy, particularly during colonic or rectal surgery when the liver may not be fully exposed, and proof of metastastic disease by histology was not possible in all patients with only impalpable lesions.

In this study, intraoperative ultrasonography was performed using a sector scanner rather than a linear array. The main advantage of this technique was that a wider field of view was obtained. Intraoperative ultrasonography was used within the setting of a 'colonic resection' and not as an aid to hepatic resection.

Intraoperative ultrasonography of the liver is probably of

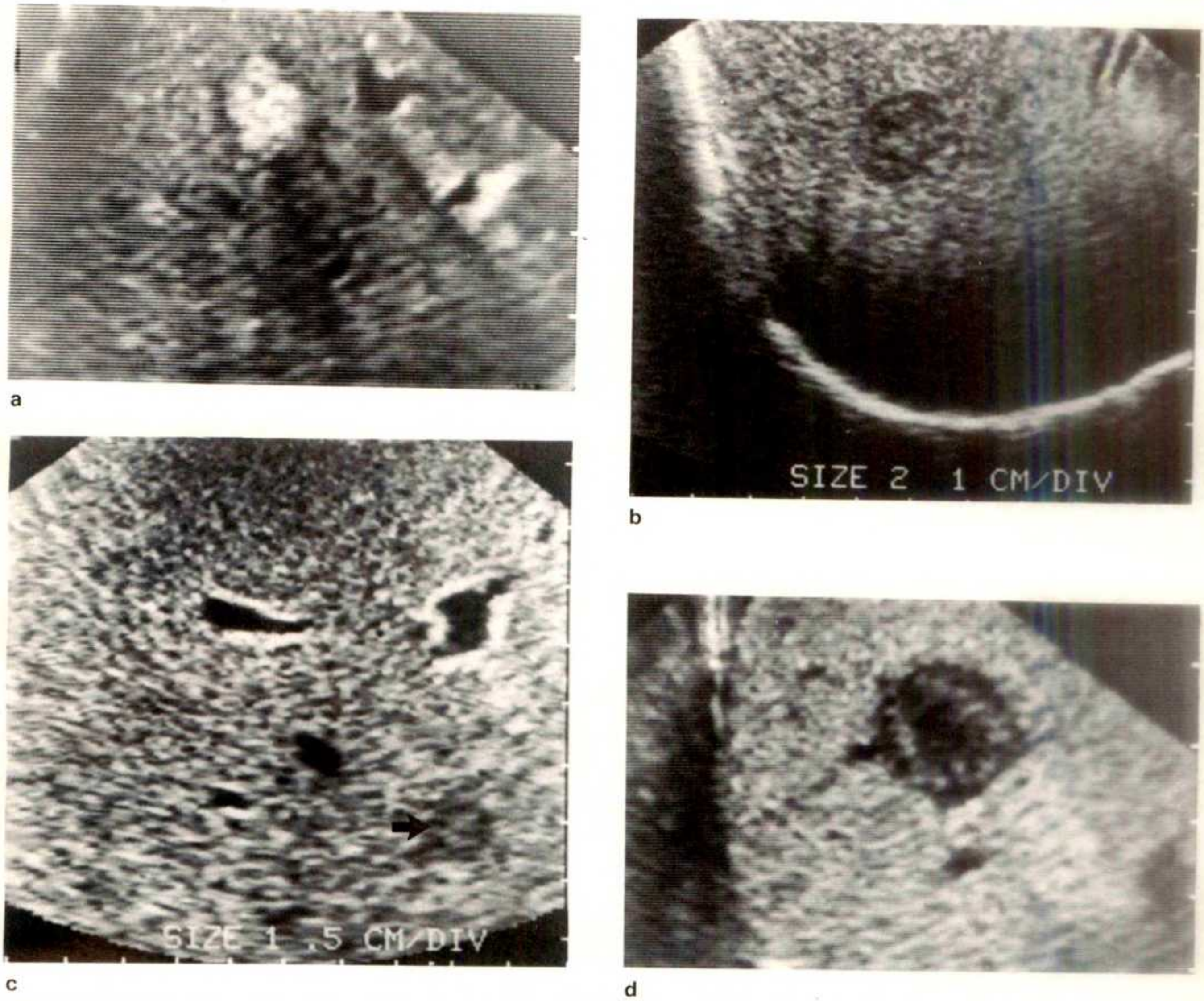

Figure 1 *Impalpable liver metastases detected by intraoperative ultrasonography.* **a** *Hyperechoic;* **b** *isoechoic;* **c** *isoechoic (metastases arrowed);* **d** *hypoechoic*

most value to surgeons as an aid to hepatic resection[9,10] but it has also been used to monitor hepatic cryotherapy[11,12]. The routine use of intraoperative ultrasonography during colorectal surgery would depend on its accuracy, performance against other imaging techniques, ability to change patients' management and cost effectiveness.

This study shows that colorectal metastases (as small as 5 mm in diameter) can be detected using intraoperative ultrasonography and that in 50 per cent of patients with palpable metastases more liver metastases are detected by intraoperative ultrasonography. Intraoperative ultrasonography detected impalpable metastases in six patients in whom liver palpation was normal. Two of three patients would have been suitable for liver resection if, at the time of proposed resection, further metastases had not been found, rendering the disease unresectable. In one additional patient intraoperative ultrasonography rendered resectable disease unresectable by demonstrating metastases beyond the proposed limit of resection.

The accuracy of abdominal ultrasonography and CT scanning in the detection of colorectal liver metastases has been studied previously[13–15]. CT scanning is probably more accurate, less observer dependent and provides the surgeon with an anatomical representation of the position of the metastases[16]. It has a sensitivity of only 70–80 per cent, however, when palpation is used as the gold standard and may miss half of the lesions less than 2 cm in diameter detectable at operation[17]. Preoperative abdominal ultrasonography misses more metastases of less than 2 cm than were missed by CT scanning[14]. CT scanning performed after intrahepatic arterial injection of iodized oil (Lipoidol, May and Baker, Dagenham, UK)[18] or rapid magnetic resonance imaging which dispenses with movement-related problems[19] may prove useful for the detection of metastases in future.

Intraoperative ultrasonography is a simple technique for the examination of the liver for metastases. It increases the number of metastases detected and identifies small metastases that are missed by palpation, abdominal ultrasonography and CT scanning.

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Effect of fibrin sealant on the healing colonic anastomosis in the rat

A. C. van der Ham, W. J. Kort, I. M. Weijma, H. F. G. M. van den Ingh* and J. Jeekel

*Laboratory for Experimental Surgery, Erasmus University, Rotterdam and *Department of Pathology, St. Clara Ziekenhuis, Rotterdam, The Netherlands*

Correspondence to:
Dr A. C. van der Ham, Laboratory for Experimental Surgery,
Dr. Molewaterplein 50, PO Box 1738, 3000 DR Rotterdam,
The Netherlands

Fibrin adhesives have been advocated as a protective seal in colonic anastomosis to prevent leakage. In order to assess the effect of fibrin glue sealing we compared the healing of sutured colonic anastomosis in the rat (group 1) with the addition of human-derived fibrin sealant (group 2). As a control for a possible reaction to foreign protein, in group 3 the sutured anastomosis was sealed with specially prepared rat fibrin adhesive. On days 2, 4 and 7, ten animals in each group were killed. Adhesion formation was scored and the in situ *bursting pressure was measured. The collagen concentration and degradation were estimated by measuring hydroxyproline. Adhesion formation was significantly increased in groups 2 and 3 compared with the control group. On days 2 and 7 the bursting pressure was not different between the groups. On day 4 the bursting pressure in groups 2 and 3 was significantly lower than in group 1 (*P<0·001*). These findings correspond with the results of collagen measurements. On day 4 the concentration of hydroxyproline was significantly reduced in groups 2 and 3. Histological examination showed infiltration of neutrophilic granulocytes into the sealant on days 2 and 4; on day 7 the sealant had vanished. From these results it is concluded that fibrin sealing of the colonic anastomosis in the rat does not improve healing, as demonstrated by bursting pressure and hydroxyproline concentration. On the contrary, it seems to have a negative influence.*

Leakage from a colonic or rectal anastomosis is a major complication after surgery with a reported incidence of up to 50 per cent[1]. It is associated with a significantly increased mortality and morbidity[2]. Many factors are reported to contribute to the healing of or leakage from an anastomosis, such as blood supply, oxygen tension, tension-free anastomosis, type of sutures or staples, surgical technique and bowel preparation[2–4]. All these factors have in common the fact that they influence the synthesis of new or degradation of old collagen, the key product in wound healing[4].

The quantity and quality of collagen in the submucosal layer of the intestinal wall determines the strength of the healing intestine[5]. Many studies on collagen metabolism in intestinal anastomosis have been performed using a rat model[6–8]. Following the construction of an anastomosis in the colon there is a significant decrease in collagen[9–11]. This decrease in collagen content is highest just proximal to the anastomosis. During the early phase of healing there is increased breakdown of mature collagen in combination with increased synthesis of new collagen[11]. Local degradation of mature collagen might be the cause of cutting through of sutures thus causing breakdown of the anastomosis[8,12]. Using tritiated proline Cronin *et al.* observed that, during the first 5 days, destruction of old collagen takes place in the entire colon, with its maximum near the anastomosis outweighing the formation of new collagen[13].

Collagen is very resistant to the action of proteolytic enzymes, but breakdown is initiated by the specific enzyme collagenase. A significant increase in collagenase was found in the gastrointestinal tract after anastomosis in the colon[14]. An experiment using aprotinin, a protease inhibitor, showed a significant increase in bursting pressure of colonic anastomoses in rabbits[15–17]. Factors directly influencing the activity of collagenase are bacteria and inflammation around infected anastomoses[11,18]. In addition, inflammatory cells are known to produce collagenase[19].

Fibrin sealant is a multicomponent biological adhesive made of concentrated human fibrinogen which can be used to establish haemostasis or as an adhesive in wound repair. Several studies have shown that fibrin sealant contributes favourably to wound healing by producing local haemostasis and by stimulating the influx of macrophages that produce factors causing angiogenesis, fibroblast proliferation and collagen production[20–22]. It has been shown that by sealing an intestinal anastomosis bacteria can be confined intraluminally, thus reducing perianastomotic inflammation[23]. Furthermore, fibrin sealant contains the protease inhibitor aprotinin in order to reduce fibrin degradation. Additional sealing has been advocated in normal and high-risk colonic anastomosis in humans as a method of preventing anastomotic leakage[24–28]. However, experimental studies are conflicting and prospective randomized clinical studies are lacking[29,30]. The aim of the present study was to determine the effect of fibrin sealing on healing of normal anastomoses in the rat.

Materials and methods

Ninety male Wag/Rij rats, weighing 180–230 g, were randomly allocated to three treatment groups and were allowed water (acidified, pH 3·0) and food (AM II, Hope Farms, Woerden, The Netherlands) *ad libitum* before and after operation. Operations were performed using ether anaesthesia. Through a midline incision, 1 cm of the left colon, 3 cm proximal to the peritoneal reflection, was resected. A single layer end-to-end anastomosis was performed with 12 interrupted, inverting 7/0 polypropylene (Prolene®, Ethicon, FRG) stitches in a standard fashion. The resected segment of colon was frozen and kept at –80°C until analysis to serve as an individual control.

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The study comprised the following groups: group 1, control sutured anastomosis; group 2, sutured anastomosis plus human fibrin sealant; group 3, sutured anastomosis plus rat fibrin sealant. The human fibrin sealant (Tissucol®, Immuno AG, Vienna, Austria) and rat fibrin sealant (Immuno AG, Vienna, Austria) were prepared according to the manufacturer's instructions. Fibrin sealant is a multicomponent adhesive consisting of a freeze-dried protein concentrate of human fibrinogen (120 mg/ml) which is reconstituted in a solution of aprotinin (3000 kallidinogenase inactivator units/ml) and a solution of thrombin (500 units/ml) and calcium chloride (40 mmol/l). After preheating to 37°C the components were reconstituted in their solutions and drawn up in separate syringes. These syringes were fitted in a specially designed syringe holder making it possible to mix and apply both components simultaneously. On mixing and application the fibrinogen was activated to form fibrin and the solutions were transformed into a rubber-like adhesive mass.

For one anastomosis 0·2 ml of fibrin sealant was used. On days 2, 4 and 7, ten rats from each group underwent relaparotomy. Following ether anaesthesia the laparotomy incision was reopened and the degree of adhesion formation was assessed. We used the following scale: 0, no adhesions; 1+, minimal adhesions, mainly between anastomosis and omentum; 2+, moderate adhesions, i.e. between omentum and the anastomotic site and between the anastomosis and a loop of small bowel; 3+, severe and extensive adhesions, including abscess formation[30]. Thereafter the rectum was cannulated and the left colon was ligated twice, 1 cm proximal and 1 cm distal to the anastomosis, the latter around the rectal cannula. Care was taken not to disturb the anastomosis and its adhesions. The rectal cannula was connected to an infusion pump (Hospal®, Italy), with a side arm to a pressure transducer connected to a recorder. The *in vivo* anastomotic bursting pressure was measured by infusing normal saline at a constant rate of 1 ml/min, and was marked by abrupt loss of pressure. After measuring the bursting pressure the animal was killed by intrathoracic bleeding. The left colon including the anastomosis was excised and dissected free of mesenteric fat tissue. Three rings of tissue 0·5 cm wide were cut: one ring of tissue containing the anastomosis, one ring just proximal and one ring distal to the anastomosis. For histological examination a small segment of the anastomotic ring was cut and put in 4 per cent (w/v) formaldehyde. The remaining tissue samples were immediately frozen and kept at −80°C for hydroxyproline assay.

Hydroxyproline as a measure of collagen was determined using a modified version of the colorimetric assay of Stegeman[31,32]. Collagen concentrations were calculated in μg/mg dry weight. The collagen concentration of the segment of colon resected at the initial operation served as an individual control, and was used to calculate any change in collagen content.

A segment of each anastomotic ring was cut off for histological examination and fixed in 4 per cent (w/v) formaldehyde. The samples for histology were dehydrated and embedded in paraffin. From all paraffin blocks 5 μm sections were cut and staining was performed with haematoxylin and eosin. In addition a periodic acid Schiff (PAS), a Gomori, and a Wiegert–van Gieson stain for assessment of the tissue reaction were performed. The inflammatory infiltrate (neutrophils, eosinophils, macrophages) and tissue organization (fibroblast and capillary proliferation) were scored semiquantitatively as follows: +, numerous; ±, occasionally present; −, absent.

For statistical analysis of the results, the mean values, the standard deviation and the standard error of the mean were calculated. Results were compared using the Wilcoxon rank sum test, χ^2 test and Fisher's exact test when appropriate.

Results

All animals survived the operation. Not a single animal showed macroscopic anastomotic leakage from the anastomosis at the time of reoperation. Adhesion formation was more extensive in groups 2 and 3 than in group 1 by day 4, when comparing adhesions >1 ($P = 0.02$) (*Table 1*). In groups 2 and 3 the adhesion score was highest on day 4; on day 7 fewer adhesions were noted. The maximal adhesion score was 2+ and not a single animal showed abscess formation.

The results of anastomotic bursting pressure measurements are presented in *Table 2*. On day 2 no significant differences were noted, but there was a slight increase of bursting pressure with fibrin sealant. However, on day 4 the anastomosis in the group with protection of fibrin sealant was significantly weaker compared with the control group ($P < 0.001$). Also in group 3 anastomotic bursting pressure was significantly lower ($P = 0.001$) on day 4 compared with the control group. On day 7 the difference in anastomotic bursting pressure had disappeared in both groups.

Table 1 *Adhesions following colonic anastomosis in the rat*

	Day 2		Day 4		Day 7	
Group	0–1	2–3	0–1	2–3	0–1	2–3
1 (control)	6	4	9	1 * †	6	4
2 (fibrin seal)	5	5	4	6 *	6	4
3 (rat fibrin)	2	8	1	9 †	4	6

Adhesions were graded as follows: 0–1, no to minimal adhesions; 2–3 moderate to severe adhesions; * $P = 0.02$, † $P < 0.001$, Fisher's exact test

Table 2 *Anastomotic bursting pressure of colonic anastomosis in the rat*

Group	Day 2	Day 4	Day 7
1 (control)	51(13)	123(12) *	193(8)
2 (fibrin seal)	72(10)	65(6) *	195(6)
3 (rat fibrin)	41(8)	84(10) *	176(8)

Results are given as mean(s.e.m.) values in mmHg; * $P = 0.001$, Wilcoxon rank sum test

Table 3 *Point of rupture on testing anastomotic bursting pressure*

	Day 2			Day 4			Day 7		
Group	P	A	D	P	A	D	P	A	D
1 (control)	0	10	0	0	8	2	8	0	2
2 (fibrin seal)	0	10	0	0	10	0	7	1	2
3 (rat fibrin)	0	10	0	0	10	0	9	1	0

P, proximal to anastomosis; A, anastomosis; D, distal to anastomosis

On day 2 bursting invariably occurred at the anastomosis (*Table 3*). On day 4 in the control group 80 per cent of bursting occurred at the anastomosis; in groups 2 and 3 all bursting occurred at the anastomosis. On day 7 in group 1 the bursting invariably occurred outside the anastomosis; in each of groups 2 and 3 the anastomosis was the place of rupture in one animal. Bursting was most likely to take place proximal to the anastomosis in 80 per cent, 70 per cent and 90 per cent, in groups 1, 2 and 3 respectively. On day 7 the colon wall was significantly weaker proximal to the anastomosis compared with the distal colon ($P < 0.01$; Wilcoxon rank sum test).

The values of hydroxyproline concentration around the anastomosis and relative change as compared with individual normal values are presented in *Table 4*. Hydroxyproline concentration was lowest on day 2 in all groups (*Figure 1*). The relative loss of collagen was prominent in all groups except for group 3 distal to the anastomosis on day 7. Proximal to the anastomosis on day 4 and day 7, collagen decrease in group 2 was significantly higher than in group 1 (*Figure 1a*). In all groups and on all days, collagen loss was more marked proximally than distally.

Collagen loss at the anastomosis was maximal on day 2 measuring 52 per cent and 54 per cent in groups 2 and 3 respectively. On day 4 collagen decrease was higher in groups 2 and 3 than in group 1 ($P < 0.05$) (*Figure 1b*). On day 7 this difference had disappeared again.

Distal to the anastomosis, collagen change was less pronounced compared with the anastomosis and proximal part on all days (*Figure 1c*). However, also in this part on day 4 collagen decrease in groups 2 and 3 was significantly higher than in group 1. Overall there were slight differences in relative collagen loss between groups 2 and 3; however, the differences between these did not reach statistical significance.

Histological examination showed remnants of fibrin glue

Table 4 *Mean concentration (μg/mg dry weight) and relative change (per cent) of hydroxyproline in colonic anastomosis in the rat*

		Day 2		Day 4		Day 7	
	Group	Concentration (μg/mg)	Relative change (%)	Concentration (μg/mg)	Relative change (%)	Concentration (μg/mg)	Relative change (%)
Proximal to anastomosis	1	91(8·2)	−49	109(7·4)	−29 *	158(11·8)	−7·4 †
	2	82(5·4)	−50	85(8·8)	−47	102(3·7)	−38
	3	96(6·7)	−28	101(5·4)	−30	124(2·9)	−11
Anastomosis	1	97(5·5)	−44	113(5·7)	−26 *	152(7·4)	−11
	2	77(5·9)	−52	81(9·2)	−49	139(3·4)	−15
	3	61(4·3)	−54	79(6·4)	−45	131(4·4)	−6·2
Distal to anastomosis	1	135(10·1)	−22	146(7·0)	−5·7 *	157(11·2)	−7·8
	2	131(5·5)	−19	130(4·8)	−19	144(3·2)	−11
	3	114(5·7)	−15	108(4·8)	−24	140(4·8)	+1·0

Values are mean(s.e.m.); relative change is percentage of individual control value; * $P<0{\cdot}05$, † $P<0{\cdot}001$, Wilcoxon rank sum test

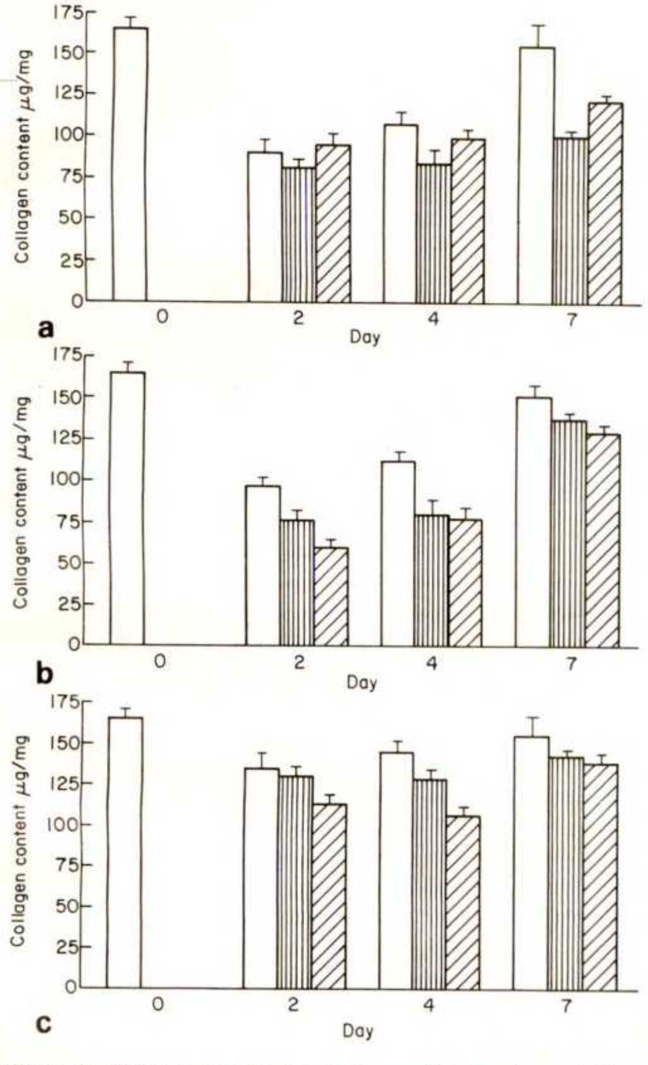

Figure 1 *Collagen content (μg hydroxyproline/mg dry weight)* **a** *proximal to colonic anastomosis,* **b** *in anastomotic area,* **c** *distal to colonic anastomosis. The column on day 0 represents normal colon tissue: ☐, control; ▥, fibrin glue; ▨, rat fibrin*

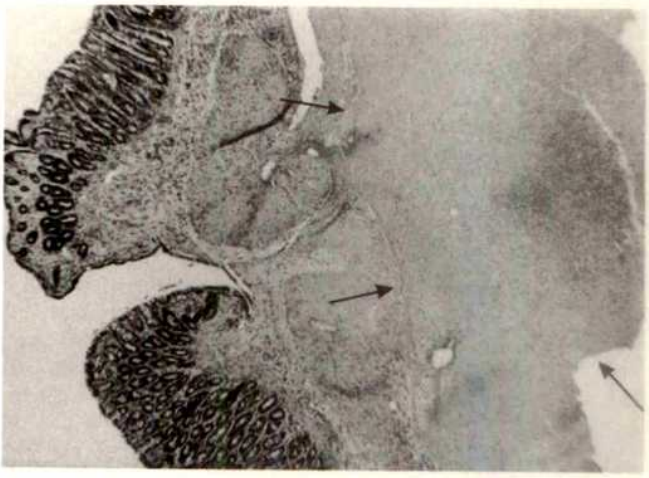

Figure 2 *Four-day-old colonic anastomosis showing fibrin seal on the peritoneal side (arrows). The submucosa shows slight oedema and cellular infiltrate. Massive cellular infiltrate is present in the fibrin seal. Haematoxylin and eosin stain. Original magnification × 50*

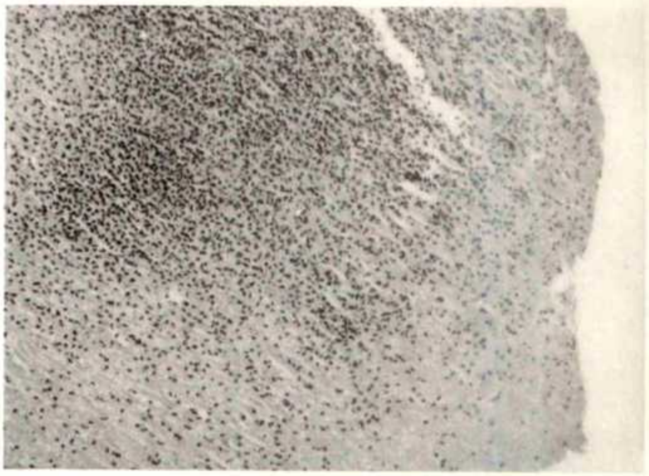

Figure 3 *Fibrin seal of 4-day-old colonic anastomosis, showing infiltration of neutrophilic granulocytes. Haematoxylin and eosin stain. Original magnification × 160*

outside the anastomosis on days 2 and 4 (*Figure 2*); on day 7, however, this fibrin was no longer demonstrated. Invariably on days 2 and 4 the fibrin seal was heavily infiltrated and surrounded by neutrophilic granulocytes (*Figure 3*). The intestinal wall showed influx of neutrophilic and eosinophilic granulocytes and macrophages on day 2 (*Table 5*). On day 2 fibroblasts were only occasionally present. On days 4 and 7 macrophages and fibroblasts were abundant in all groups while granulocytes were again reduced in number. On day 7, however, the presence of macrophages had increased in group 2 compared with group 1 ($P<0{\cdot}02$). No differences were noted in the number of fibroblasts and capillary proliferation.

Discussion

Additional sealing has been advocated in normal and high-risk colonic anastomoses in patients as a method to prevent

Table 5 *Presence of different cell types in the healing colonic anastomosis in the rat*

		Day 2			Day 4			Day 7		
Cell type	Group	+	±	–	+	±	–	+	±	–
Neutrophils	1	2 *	4	1	0 *	5	3	1	1	7
	2	8	0	0	8	0	0	2	3	3
	3	9	0	0	7	0	0	2	3	2
Eosinophils	1	6	1	0	1	6	1	4	3	2
	2	5	1	2	5	1	2	1	4	3
	3	4	5	0	3	4	0	0	5	2
Macrophages	1	3	4	0	4	4	0	4 †	5	0
	2	4	3	1	7	1	0	8	0	0
	3	2	6	1	3	4	0	4	3	0
Fibroblasts	1	0	4	3	8	0	0	8	1	0
	2	3	2	3	6	2	2	7	1	0
	3	0	3	6	4	3	0	7	0	0

+,Numerous; ±, occasionally present; –, absent; * $P<0{\cdot}01$, † $P=0{\cdot}02$, χ^2 test

anastomotic leakage[24–28]. However, experimental studies are conflicting and prospective randomized clinical studies are lacking[29,30]. We performed the present study in order to investigate the influence of fibrin sealant on the healing colonic anastomosis in the rat, with regard to intraperitoneal adhesion formation, mechanical strength, collagen metabolism and histological appearance. The application of fibrin sealant (human as well as rat fibrinogen) resulted in increased adhesion formation around the anastomosis on day 4. On day 7 this difference was not prominent. We did not find increased abscess formation as reported by Houston and Rotstein[30]. In fact in the present series no abscesses at all were found, while these authors reported abscess formation in 20 per cent in their control group and nearly 100 per cent following fibrin sealing. An important factor accounting for these differences in results might be the use of silk suture material in their study, while in the present study monofilament polypropylene was used. Quality of technique may also account for this difference. In the authors' opinion fibrin sealant *per se* cannot be held liable for abscess formation in colonic anastomosis.

Application of human as well as rat fibrinogen did not result in an elevation of anastomotic bursting pressure during the first 7 days of healing, contrary to expectations. Surprisingly a statistically significant lower bursting pressure was observed on day 4. This effect seems to be only temporary and had disappeared by day 7. As a consequence the sealed anastomosis can be considered weak during the critical period of healing. This negative effect on the mechanical strength of colonic anastomoses corresponds with one other rat study[30]. The mechanical weakness of the sealed 4-day anastomosis is especially alarming as this is the time when leakage threatens.

After sealing, collagen concentration within the anastomosis and proximal and distal to the anastomosis was lower on day 4. On day 7 this difference was still apparent, but exclusively proximal to the anastomosis. The significantly lower bursting pressure on day 4 in the sealed anastomosis in groups 2 and 3 corresponds with a statistically significant decrease in collagen concentration. This decreased collagen concentration may account for the lower bursting pressure because the bursting pressure is mainly dependent on submucosal collagen[11]. The finding of asymmetrical collagen changes around the anastomosis has been reported in other studies[11,33]. We also were able to demonstrate that collagen changes are more marked proximally than distally. This may explain why rupture took place almost exclusively proximal to the anastomosis on testing the bursting pressure on day 7. No good explanation has so far been given for the cause of this phenomenon.

Histological examination showed excessive accumulation of neutrophil granulocytes in the fibrin seal covering the anastomosis on days 2 and 4. Although no abscesses or pus were noted, both human and rat fibrinogen gave rise to infiltration of granulocytes. This finding suggests that local fibrin deposition predisposes to local infection and inflammation. Under normal conditions deposition of fibrin is a normal phenomenon of wound healing and within 3 h the wound is infiltrated by granulocytes, followed by macrophages during the first 24 h[34]. The presence of foreign material, e.g. fibrin or bacteria, can prolong the inflammatory phase. It may be that the application of fibrin sealant provides a site for bacterial proliferation. Using germ-free rats a significant reduction in the lowering of hydroxyproline concentration around the anastomosis was observed by Mastboom *et al.*[35].

Inside the intestinal wall macrophages were more abundant near the anastomosis on day 7 after application of fibrinogen; however, these cells were not very prominent on days 2 and 4. Neutrophil granulocytes, macrophages and bacteria are known sources of proteolytic enzymes including collagenase and might cause increased collagen breakdown in the intestinal wall. The postoperative decrease of breaking strength of colonic anastomoses is prevented in rats with neutropenia[36]. It seems likely that in the present model the increased number of neutrophils in direct contact with the anastomosis was responsible for the increased loss of hydroxyproline in the colonic wall after the addition of fibrin seal.

Another possible explanation may be the formation of a physical barrier around the anastomoses by fibrin sealant. Wrapping of colonic anastomoses in Silastic® (Dow Corning, Reading, UK) sheeting results in leakage and high mortality because of separation of the anastomosis from the peritoneal defences[37]. Fibrin sealing might separate the anastomoses from the defence mechanisms of the peritoneum analogous to wrapping in Silastic.

The present results do not show enhanced healing of colonic anastomosis following sealing with fibrin glue, contrary to other studies[24–28]. Our findings give support to the conclusion of Houston and Rotstein that the application of fibrin on colonic anastomosis may lead to delayed healing[30]. These authors postulated that the negative effect of human fibrin sealant is caused by a reaction to foreign protein. In order to evaluate this mechanism we used sealant made of rat fibrinogen in a distinct control group. Using rat fibrinogen the same impeding effect as with human material was observed.

From these results we may conclude that fibrin sealing of normal colonic anastomoses in the rat does not improve the healing process; on the contrary, it has a negative influence during the first week. As a consequence, the routine use of fibrin sealant in non-complicated intestinal anastomoses in the clinical situation does not seem justified. Whether this is also true for high-risk anastomoses, e.g. those associated with peritonitis or ischaemia, is subject to further study.

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Influence of methylprednisolone on the healing of intestinal anastomoses in rats

W. J. B. Mastboom, T. Hendriks, B. M. de Man and H. H. M. de Boer

Department of General Surgery, St. Radboud University Hospital, Nijmegen, The Netherlands

Correspondence to:
Mr W. J. B. Mastboom,
Department of General Surgery,
St. Radboud University Hospital,
PO Box 9101, 6500 HB Nijmegen,
The Netherlands

Although steroids are generally thought to impair intestinal anastomotic healing, this effect has never been proven unequivocally in either clinical or experimental studies. We have investigated the influence of methylprednisolone (2·5 or 10·0 mg kg^{-1} day^{-1}) given from 2 days before operation onwards, on 3-day-old and 7-day-old ileal and colonic anastomoses in rats. Anastomotic abscesses occurred more frequently in the ileum, but not in the colon, after steroid medication. However, methylprednisolone did not lower anastomotic bursting pressures in either of the bowel segments. Comparison of the hydroxyproline content of the anastomotic segment yielded no significant difference between control and methylprednisolone groups in either small or large bowel. Thus, healing of experimental colonic anastomoses remains unaffected by short-term administration of this corticosteroid.

Healing of intestinal anastomoses and the factors influencing this process remain a worthwhile subject for experimental and clinical study, since in humans anastomotic dehiscence is associated with a high mortality rate. In general, steroid medication is believed to be one of the factors which increase the risk of anastomotic leakage[1,2]. In two large retrospective clinical studies a negative influence of corticosteroid medication on anastomotic healing could not be demonstrated[3,4].

The idea that steroids are detrimental to anastomotic repair is mainly based on experimental studies on skin wounds[5–7]. However, it has been emphasized by several authors that it must not be taken for granted that wounds in other tissues react similarly[8,9]. Few investigations have been reported on the influence of steroids on intestinal healing The data available on the alimentary tract indicate that administration of steroids impairs healing of gastric and duodenal incisional wounds[10] and suggest a negative influence on mechanical strength of anastomoses in jejunum[11] and colon[12] If steroid medication indeed affects healing of intestinal anastomoses, one would expect this to be reflected in both anastomotic strength and the postoperative collagen metabolism around the anastomosis.

In the present study, we have investigated the influence of methylprednisolone on mechanical strength and hydroxyproline content of anastomoses in small and large bowel of rats.

Materials and methods

Animals

Sixty male Wistar rats weighing between 200 and 270 g were divided into three equal groups The two medically treated groups received, respectively, 2·5 mg kg^{-1} methylprednisolone day^{-1} (MP-2·5 group) and 10·0 mg kg^{-1} methylprednisolone day^{-1} (MP-10 group), and the remaining group served as control, receiving an equal dose of isotonic saline. The animals were fed a standard diet (Hope Farms, Woerden, The Netherlands) and allowed water *ad libitum*.

Methylprednisolone

Doses of methylprednisolone, 2·5 mg kg^{-1} day^{-1} and 10·0 mg kg^{-1} day^{-1}, were chosen from doses used in previous studies[5–7,11,13,14] and are believed to suppress inflammatory reactions in rats effectively In a pilot study, it was established that neither dose caused mortality in unoperated rats over a period of 15 days. Daily doses of placebo and medication, dissolved into 0·1 ml isotonic saline, were administered intramuscularly into one of the thighs of the hind legs Dosage was started 2 days before operation and maintained until the day of killing

Operative procedure

Operations were performed as described before[15]. Briefly, after induction of anaesthesia with sodium pentobarbital and a median laparotomy, 1 cm of both ileum and colon were resected at 15 cm proximal to the ileocaecal junction and 3 cm proximal to the rectal peritoneal reflection, respectively. An inverting one-layer end-to-end anastomosis was constructed microsurgically with monofilament nylon (8/0, Ethicon Ltd., Edinburgh, UK). After 3 or 7 days the rats were killed by an intracardiac overdose of sodium pentobarbital. Approximately 5 cm of intestine containing the anastomosis was removed, leaving surrounding tissue untouched, in order to measure the bursting pressure. Subsequently, a 1 cm segment with the anastomosis in the middle was removed to determine the collagen content

All samples were frozen immediately and stored in liquid nitrogen until further processing.

Bursting pressure

After careful removal of faeces, the bowel segment was attached to an infusion pump, which was filled with methylene blue-stained saline solution (0·9 per cent) During pressure measurement, the pressure was raised with an infusion rate of 2·5 ml min^{-1} Leakage was recorded immediately by loss of pressure. The site of the lesion, indicated by effusion of methylene blue into the water, was noted

Analytical procedures

The samples were pulverized in liquid nitrogen, lyophilized and kept at −30°C for analysis

The dry weights of control segments and the samples containing the anastomosis were determined. In all samples the hydroxyproline content, as a measure for the collagen level, was measured as described previously[16].

Statistical methods employed are mentioned with the results

Results

Neither free anastomotic perforation nor premature mortality was observed among the experimental groups. However, there were significantly more ileal anastomotic abscesses in both corticosteroid-treated groups (*Table 1*) in comparison with the control group, while abscesses around colonic anastomoses were only found on one occasion.

The course of postoperative body-weight change was similar in all groups. After an average loss of some 12 per cent between the second and fourth day after operation, body-weight increased up to the preoperative level on the seventh day

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Table 1 *Abscess formation around ileal anastomoses*

Group	n	Day 3	Day 7	Total
Control	20	1	0	1
MP-2·5	20	4	3	7*
MP-10	20	5	5	10†

Differences between control and methylprednisolone (MP) groups were tested for significance using Fisher's exact test, * $P<0·05$; † $P<0·01$

Table 2 *Bursting pressures (mmHg) in ileal and colonic anastomoses*

Group	n	Day 3	n	Day 7
Ileum				
Control	6	63(14)	10	201(62)
MP-2·5	8	72(26)	10	227(60)
MP-10	10	57(22)	10	209(51)
Colon				
Control	9	109(54)	10	149(21)
MP-2·5	10	90(40)	10	178(36)*
MP-10	8	99(39)	10	187(24)†

Levels of significance for the differences between the groups were calculated by means of a Wilcoxon two-sided unpaired test. Significant differences are only found in colon at day 7 between control and methylprednisolone (MP) groups; * $P<0·05$; † $P<0·01$ Values are given as mean(s.d.)

Table 3 *Mean hydroxyproline content (μg cm^{-1}) in ileal anastomotic segments. The last column represents the ratio between anastomotic and control segments*

Group	Day after operation	Control segment	Anastomotic segment	Ratio
Control	3	94(27)	166(27)	1·8(0·4)
	7	86(31)	235(70)	2·8(0·6)
MP-2·5	3	89(39)	143(43)	1·7(0·4)
	7	87(31)	270(58)	2·9(0·7)
MP-10	3	112(26)	161(38)	1·4(0·2)*
	7	79(30)	223(52)	2·8(0·9)

Presence of significant differences between control and both methylprednisolone (MP) groups was calculated by means of a Kruskal–Wallis K-sample test. Levels of significance between the individual groups were calculated using a Wilcoxon two-sided unpaired test. * Ileum ratio. MP-10 *versus* control, $P<0·05$; MP-10 *versus* MP-2·5, $P<0·05$ Values expressed as mean(s.d.)

Table 4 *Mean hydroxyproline content (μg cm^{-1}) in colonic anastomotic segments The last column represents the ratio between anastomotic and control segments*

Group	Day after operation	Control segment	Anastomotic segment	Ratio
Control	3	124(36)	252(45)	2·2(0·6)
	7	114(15)	264(54)	2·4(0·7)
MP-2·5	3	122(45)	216(42)	2·3(1·0)
	7	128(49)	240(52)	2·0(0·6)
MP-10	3	135(23)	216(34)	1·6(0·3)
	7	125(33)	233(39)	2·0(0·1)

No significant differences between control and methylprednisolone (MP) groups were found using a Kruskal–Wallis K-sample test Values expressed as mean(s.d.)

During collection of the anastomotic segments after killing 3 days after operation, dehiscence of some anastomoses occurred and as a consequence their bursting pressure could not be measured. Bursting pressures of the remaining anastomotic segments are presented in *Table 2*. At day 3 both ileal and colonic segments burst at the anastomosis, without significant differences between the groups. At day 7 all perforations occurred outside the anastomotic area. However, significant differences were found for colonic segments, where bursting pressures in the treated groups were significantly higher than in the control group.

Tables 3 and *4* give the hydroxyproline content of the anastomotic and control segments, together with their ratio, in ileum and colon, respectively. No differences between groups were found in control segments obtained at the original operation in either ileum or colon. The mean hydroxyproline content in uninjured colon was 30 per cent higher than in uninjured ileum. The hydroxyproline content of anastomotic segments is always higher than that of control segments of equal length, since they contain a greater length of intestinal wall because of the inversion used to construct the anastomosis.

In the ileum, a significant rise in anastomotic hydroxyproline level was observed between 3 and 7 days after operation. This occurred in all three groups and no effect of methylprednisolone was apparent, with one exception; comparison of the ratios between anastomotic and control hydroxyproline content showed a significantly lower ratio in the high-dose methylprednisolone group 3 days after operation (*Table 3*).

In the colon (*Table 4*), the hydroxyproline content of 7-day-old anastomoses was not elevated with respect to that in 3-day-old anastomoses. Here, no significant differences were found between control and methylprednisolone groups.

Discussion

Experimental studies have shown that corticosteroids impair wound healing in skin[5–7,14,17]. Comparison of the results from these studies is hampered by the fact that they differ in many respects, such as compound used, dose and time and method of administration. For the present study we chose methylprednisolone in a dose (10 mg kg^{-1} day^{-1}) which inhibits development of granulation tissue in rats[13,14]. Neither this dose, nor the lower dose used, resulted in a loss of strength of anastomotic segments in either ileum or colon (*Table 2*).

Very few data are available on the effect of steroids on anastomotic repair. Aszodi and Ponsky found a significant reduction in bursting pressure of jejunal anastomoses in rats which had been treated with hydrocortisone (5 mg kg^{-1} day^{-1}) from 14 days before operation onwards[11]. However, at the time of operation these animals had lost 15 per cent of their bodyweight, which raises the question whether the delay in recovery of strength was the result of malnutrition rather than a direct effect of corticosteroid action. Very recently, Houston and Rotstein reported that administration of methylprednisolone, in a dose of 25 mg kg^{-1} day^{-1}, which would be an extremely high dose in human terms, significantly reduced colonic strength[12]. This treatment also increased the incidence of perianastomotic abscess formation from 20 to 58 per cent. We found only one case of abscess formation in the 60 colonic anastomoses constructed in the various groups. In contrast to this finding in colon, steroid administration led to a significant rise in the number of abscesses in ileal anastomoses (*Table 1*). It seems not unlikely that methylprednisolone suppresses the immune system and inhibits the antibacterial functions of leucocytes[18], which could eventually result in enhanced abscess formation However, it remains unclear why the incidence of colonic abscesses was not increased, unless one assumes that defence mechanisms are more highly developed in the colon, perhaps because of its greater intrinsic bacterial population.

Since collagen provides structure and strength to the intestinal wall, postoperative collagen metabolism is generally thought to be crucial to the development of anastomotic strength. Inflammatory cells may strongly affect collagen metabolism: polymorphonuclear granulocytes and macrophages contain collagenolytic enzymes[18,19] while macrophages also regulate fibroplasia[18]. Thus, corticosteroids as potent suppressors of migration and function of these cells could very well affect degradation and synthesis of anastomotic collagen. Furthermore, direct effects of glucocorticoids on collagen synthesis have been amply demonstrated[20] and methylprednisolone, used in doses similar to those employed by us[21], indeed lowered accumulation of collagen in granulation tissue of rats.

However, methylprednisolone did not affect the amount of hydroxyproline present in colonic anastomoses, neither when the content in the anastomotic segment was compared nor when the ratio between anastomotic and control segments was used as a parameter. In the ileum, there was only a reduction in the ratio between anastomotic and control segments at 3 days in the high-dose group. This effect might possibly be explained by the relatively high values measured in the control segments from this group. Altogether, the effects of methylprednisolone administration on anastomotic collagen content in the intestine appear to be of limited significance and to have no consequence for anastomotic strength in the rat.

Thus, it is apparent that short-term administration of corticosteroids, in doses which have been shown to affect healing in other tissues, does not impair the development of intestinal anastomotic strength. Colonic repair does not appear to suffer at all, while in ileum only abscess formation increases. It remains to be demonstrated if such abscesses may eventually result in anastomotic dehiscence. As a consequence, we conclude that the premise that steroid medication is essentially detrimental to (colonic) anastomotic repair should not be taken for granted.

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Influence of local hyperthermia on the healing of small intestinal anastomoses in the rat

T. Shimizu, M. Maeta and S. Koga

First Department of Surgery, Tottori University School of Medicine, 36-Nishimachi, Yonago 683, Japan

Correspondence to:
Dr T. Shimizu

Peritoneal hyperthermia may have a role in limiting serosal metastatic disease. When applied to the peritoneal cavity immediately after surgery, it is important to know the optimum temperature, and to investigate the subsequent healing of intestinal anastomoses. To study the first problem, local hyperthermia was applied to the intestinal loop of rats for 30 min. Treatment at 46·0°C or 45·0°C resulted in 100 per cent and 90 per cent mortality respectively, but 100 per cent survival was obtained at 44·0°C. To study the second problem rats with intestinal anastomoses were studied in three groups: group A, local hyperthermia (44·0°C × 30 min) applied to the intestinal loop containing the anastomosis; group B, local hyperthermia (44·0°C × 30 min) applied using saline supplemented with mytomycin C (10 mg/l); group C (controls) no thermal treatment was applied. Anastomotic healing was assessed by breaking strength and histological examination. On the third day after operation, the breaking strength of anastomoses decreased to the lowest values in each group, but no statistically significant differences were noted. On the seventh and 14th day, increased resistance to breaking developed in all three groups and was greatest in the thermally treated groups. Histological findings supported these results. Local hyperthermia up to 44·0°C × 30 min had no adverse effects on the healing of intestinal anastomoses.

We have been evaluating the clinical application of continuous hyperthermic (42°C) peritoneal perfusion (CHPP) with mitomycin C (MMC, Kyowa Hakko, Tokyo, Japan) in a randomized control study[1], as a prophylactic treatment to prevent postoperative peritoneal recurrence of gastric cancer by serosal invasion. CHPP therapy resulted in a significant improvement in the survival rate of treated patients. The cytocidal effect of CHPP may be enchanced if perfusion at a higher temperature could be employed. A higher local-perfusion temperature might threaten the patient's life and may interfere with the healing of surgical wounds. In an attempt to answer these questions the present investigations were carried out.

Materials and methods

Local hyperthermia

Male Wistar rats, weighing 380–500 g were divided into three groups of ten. Each rat was anaesthetized with pentobarbital sodium, and an intact small intestinal loop of approximately 5 cm in length, at a distance of 40 cm from the terminal ileum (the total intestinal length of the rat is about 100 cm), was immersed in saline at 46·0°C, 45·0°C or 44·0°C for 30 min (*Figure 1a*). After treatment, survival rates were compared over the course of 4 months.

Operation and local hyperthermia

A total of 209 rats had an inverted, one-layer, end-to-end anastomosis made at a distance of 40 cm from the terminal ileum. It was completed microsurgically, with 20–22 stitches of running suture at a distance of 0·7 mm from the wound edges with 7–0 Proline® (Ethicon Ltd., Edinburgh, UK). The rats were subdivided into three groups. In group A ($n=76$), local hyperthermia (44·0°C × 30 min) was applied to the intestinal loop containing the anastomosis, according to the method described above. In group B ($n=45$), the thermal treatment was performed using saline supplemented with MMC (10 mg/l). In the control group, C ($n=88$), no thermal treatment was applied.

The breaking strength at the anastomosis was tested on the third,

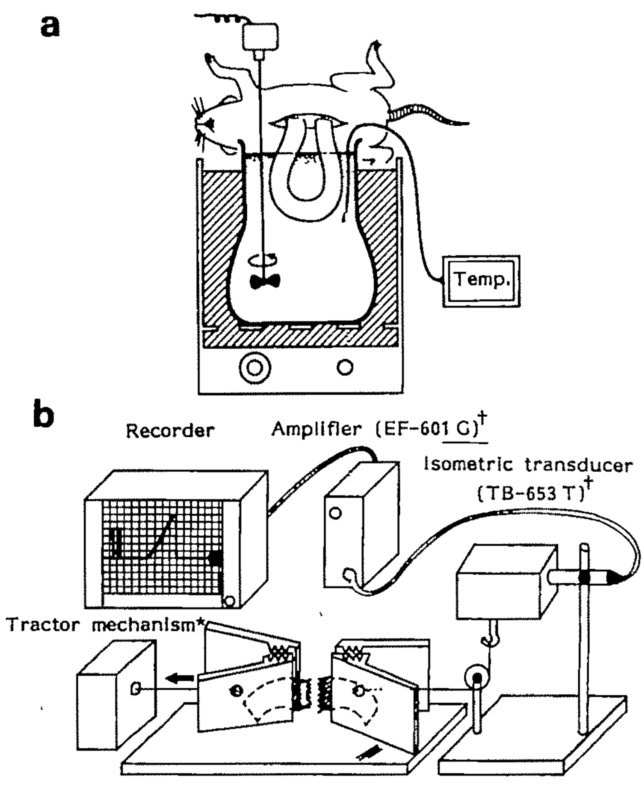
a
Temp.
b
Recorder
Amplifier (EF-601 G)†
Isometric transducer (TB-653 T)†
Tractor mechanism*
Break of the intestinal anastomosis

Figure 1 **a** *Apparatus for local hyperthermia of the small intestine at various temperatures and* **b** *schematic diagram of the tensiometer.* * *Constantly increasing force of 60 g/sec;* † *Nihon Kohden Co., Tokyo, Japan*

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seventh and 14th days and immediately after completion of the anastomosis (*Figure 1b*).

For histological preparations, an intestinal segment including the anastomosis was resected on the first, third, seventh and 14th days after operation from rats in groups A and C Longitudinal sections were cut and stained with hematoxylin and eosin, and azan to stain collagen fibres blue.

Statistical analysis was performed by Student's t test.

Results

Local hyperthermia

The survival curves of the three groups of rats are shown in *Figure 2*. Treatment at 46·0°C resulted in 100 per cent mortality within 16 days and treatment at 44·0°C resulted in 100 per cent survival. Necropsy was performed on dead rats. In almost all animals the small intestine was severely dilated on the proximal side of the treated intestinal loop and thermal damage was greater in the group treated at 46·0°C (*Table 1*).

Operation and local hyperthermia

On the third day after operation, the breaking strength in the three groups decreased to approximately 60–70 g, and no statistically significant differences were noted between three groups (*Figure 3*). On the seventh day, the breaking strength returned to the value measured immediately after operation. Remarkable increases in the breaking strength were noted in all three groups on the 14th postoperative day Significant ($P<0{\cdot}01$) increases in breaking strength were observed in groups A and B compared with that of the control group. While body-weight of rats returned to normal on the seventh day in the control groups, such recovery was significantly delayed ($P<0{\cdot}001$–$0{\cdot}02$) in the other two groups (*Figure 4*). By the 14th day the body-weight showed an upward trend in the thermally treated groups, but a statistically significant difference ($P<0{\cdot}001$) was still noted. Histological findings are shown in *Table 2*. In the first 3 days, the thermal treatment caused mucosal damage (the almost complete destruction of villi, and the occasional loss of crypts) as well as more evident infiltration of inflammatory cells at the wound edges. Fibrosis in the wound edges and thickening of the muscle layer became dominant in the thermally treated groups, at later periods (*Figure 5*).

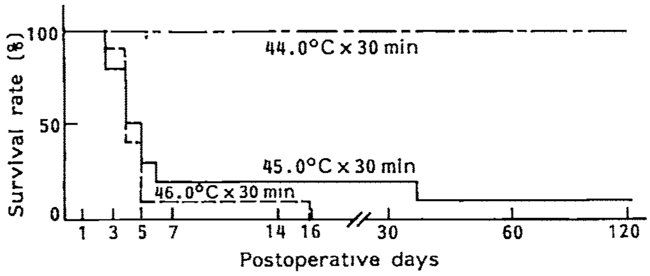

Figure 2 *Survival curve for rats treated with local hyperthermia at various temperatures*

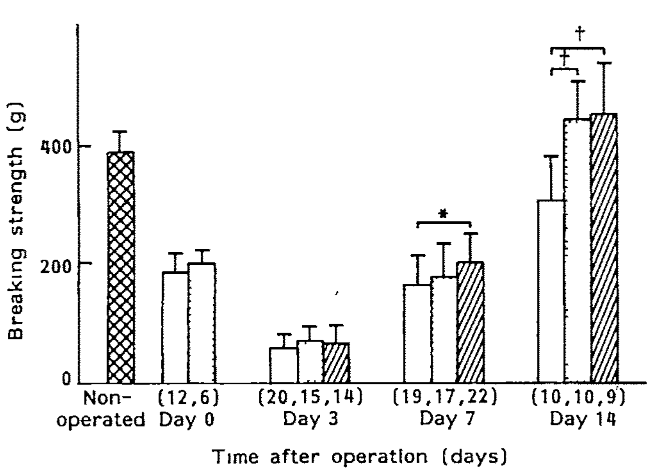

Figure 3 *Breaking strength of intestine that contained anastomoses, after local hyperthermia at 44·0°C for 30 min, with or without mitomycin C.* ▩, *Intact intestine;* □, *control* (n=*61*)*;* ⊡, *44·0°C x 30 min* (n=*48*), ■, *44·0°C x 30 min+mitomycin C* (n=*45*). *P<*0·05*. †P<*0·01 The number of experimental animals in each case is indicated in parentheses*

Table 1 *Abdominal findings from dead rats*

Treatment	Ileus	Penetration	Bleeding	Peritonitis
45·0°C x 30 min	89	22	22	0
46·0°C x 30 min	100	50	30	30

Values are percentages

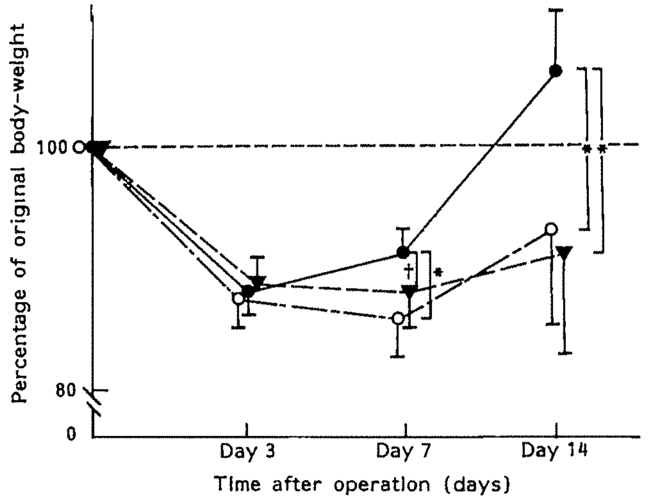

Figure 4 *Changes in body-weight of rats treated with local hyperthermia at 44·0°C for 30 min, with or without mitomycin C.* ●, *Control,* ○, *44·0°C x 30 min,* ▼, *44·0°C x 30 min+mitomycin C* †P<*0·02*, *P<*0·001*

Discussion

The first experiment showed that local hyperthermia at 44·0°C for 30 min resulted in the most effective thermal treatment without a deleterious effect on survival. The assessment of wound healing of intestinal anastomoses was made using the breaking strength at the anastomoses rather than the bursting pressure[2–4]. The timing of killing after surgery was based on the results reported previously[5–7] and special attention was paid to the third day at which time the sutures are known to have the lowest holding capacity[8]. The data showed no significant differences between three groups examined. Interference in the healing of intestinal anastomoses as a result of the local hyperthermia was not observed even in the group treated with MMC plus hyperthermia (44·0°C). We have been using MMC in solution (10 mg/l) in CHPP therapy clinically and possible adverse effects were the object of concern. At later times after operation, the recovery of mechanical strength was more rapid in the hyperthermally treated groups. The dominant fibrosis and thickened muscle layers paralleled the results of breaking strength. These histological findings may be explained by a prolongation of the inflammatory reaction at the intestinal loop caused by heating. The recovery of normal body-weight was significantly delayed in the thermally treated groups. Clinically, it seems necessary to pay special attention not so much to the possible occurrence of anastomotic leakage, but rather to the possibility of paralytic ileus in those patients who receive CHPP treatment. This study shows that local

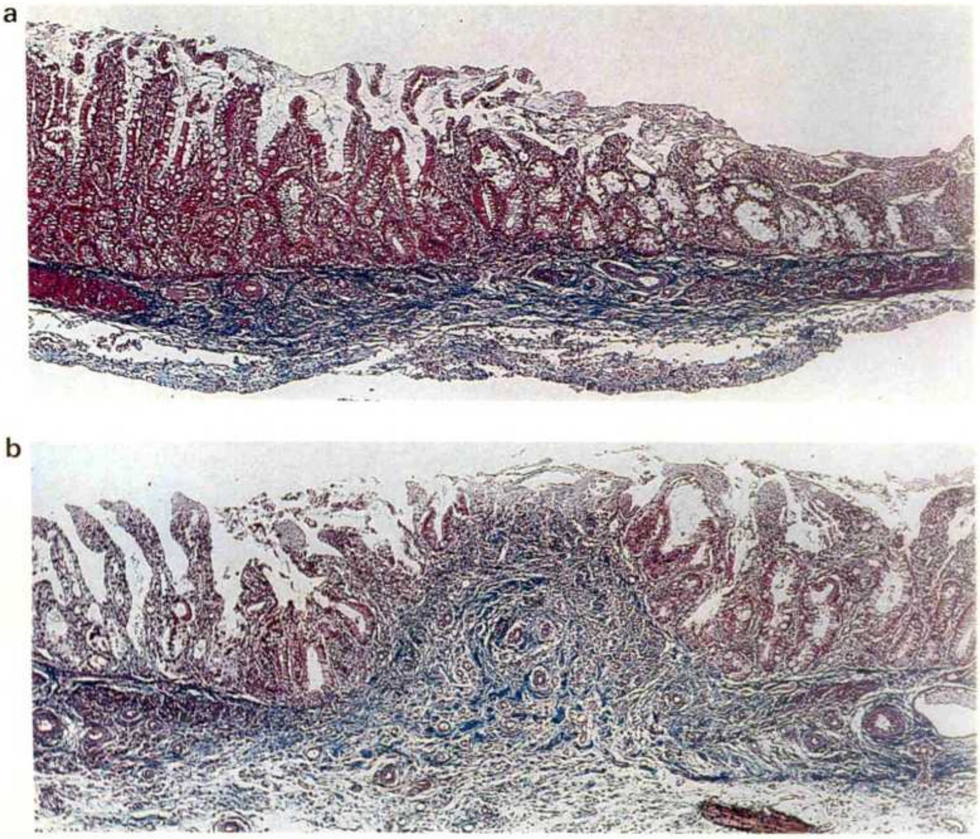

Figure 5 *Microscopic appearance of anastomotic sites after 14 days (azan, 3·3 × 4·0).* **a** *The control shows mild fibrosis that consists mainly of collagen fibres.* **b** *Relatively dominant fibrosis with thickening of the muscle layer is apparent after thermal treatment*

Table 2 *Histological findings*

	Granulocytes	Mucosal damage	Submucosal fibrosis	Muscle thickening
Day 1				
H (7)	+ + +	+ +	–	–
C (7)	+	±	–	–
Day 3				
H (5)	+ + +	+	–	–
C (8)	+	–	–	–
Day 7				
H (7)	+	+	+	–
C (4)	+	–	±	–
Day 14				
H (9)	+	–	+ +	±
C (8)	+	–	+	–

H, Hyperthermally treated group (44·0°C × 30 min); C, Control group; the number of experimental animals in each case is indicated in parentheses

hyperthermia (44·0°C × 30 min) has no adverse effect on the healing of small intestinal anastomoses. The results suggest the possibility of enchancing the clinical efficacy of CHPP therapy by perfusion at higher temperatures than have been used to date.

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Proliferation characteristics of human colorectal carcinomas measured *in vivo*

D. A. Rew,
G. D. Wilson*, I. Taylor
and P. C. Weaver†

University Surgical Unit,
Southampton General Hospital,
*Southampton, *The Gray*
Laboratory, Northwood and †St.
Mary's Hospital, Portsmouth, UK
Correspondence to:
Mr D. Rew, University Surgical
Unit, Southampton General
Hospital, Tremona Road,
Southampton SO1 6HU, UK

The cell proliferation kinetics of 100 human colonic and rectal adenocarcinomas have been studied in vivo *by bromodeoxyuridine infusion and multiparameter flow cytometry. A total of 97 patients, three with synchronous tumours, consented to receive a single bolus dose of 250 mg between 2·4 and 16 h before curative or palliative surgery. By this method, the ploidy pattern, the total and aneuploid labelling indices (LI), the S phase duration* (T_s) *and the potential doubling time* (T_{pot}) *can be estimated. Of the tumours 48 were diploid and 52 were aneuploid. The mean and median total LI of 100 tumours were 9·0 per cent (range 0·7–22·2 per cent). The mean aneuploid LI was 12·1 per cent (median 12·0 per cent, range 2·0–25·5 per cent), and was significantly higher than the total LI* ($P = 0{\cdot}01$)*. The labelling index alone is not a sufficient indicator of proliferation, because the* T_s *also varies within and between tumours. The intertumour range of the* T_s *varied from 4·0 to 28·6 h. The mean was 14·1 h and the median was 13·1 h. The mean* T_{pot} *was 5·9 days (median 3·9 days) with a range of 1·7–21·4 days. No correlation was found between any kinetic parameters and the Dukes' classification or histological classification. The correlation between proliferation and prognosis will be established in due course.*

Current prognostic indices of colorectal cancer, in practice Dukes' classification[1] and histological grade of tumour, are unable accurately to identify patients at risk of subsequent recurrence. Adjuvant treatment has as yet not been demonstrated to produce a consistent improvement in survival. It is possible that a better understanding of the proliferation characteristics of tumour cells will allow a better selection of patients suitable for adjuvant therapy, and better use of currently available treatments.

Until recently, *in vitro* radioisotope studies have been the mainstay of cell kinetic research in colorectal cancer[2–6], although studies using stathmokinetics[7] *in vivo* have been reported. The use of flow cytometry to measure the DNA content (ploidy) of fresh and archival material is well known[8–16]. A practical and safe method of *in vivo* measurement of multiple cell kinetic indices in clinical practice has been described[17,18]. Multiparameter flow cytometry can be used to measure bromodeoxyuridine (BRdUrd) uptake by S phase cells. Nuclear DNA content and ploidy, the total and aneuploid labelling indices (LI), the duration of the S phase (T_s) and the potential doubling time (T_{pot}) of tumour cells can be measured from a single injection and biopsy, and results can be obtained within 24 h. The use of BRdUrd for *in vitro* and *in vivo* studies of human colorectal tumour cell kinetics has been reported[19–21]. Khan *et al.*[20] infused BRdUrd into 14 patients with metastatic colonic adenocarcinoma. Biopsies were excised 2 h later. Labelling was of good quality and highly specific. The mean labelling index of tumours was 24 per cent (range 15·0–40·6 per cent).

The volume growth of human tumours is governed by the balance between cell production and cell loss. Flow cytometric studies reported in the literature have to date used only the total labelling index or the DNA S phase fraction (SPF) as measures of proliferation. These are static parameters which give no information on the dynamic aspects of cell production. We have measured a wider range of cell kinetic data in a series of 100 primary colorectal adenocarcinomas and compared these data with conventional prognostic indicators. The additional data regarding aneuploid labelling indices, the T_s and the T_{pot} provided by flow cytometry have not previously been evaluated in colorectal cancer. The combination of DNA ploidy and proliferation data may give a better insight into the factors influencing biological aggressiveness. We will in due course report the relationship of these data to survival.

Patients and methods

BRdUrd preparation and injection

Informed consent was obtained from all patients before intravenous injection of a single dose of 250 mg BRdUrd (Takeda Ltd., Osaka, Japan). This was dissolved in 10 ml saline solution and given over 30 s into an antecubital fossa vein. Hospital Ethical Committee permission was obtained before the study. The injection was given between 2·4 and 16 h before resection (mean 6·7 h).

Histological grading

Haematoxylin and eosin stained sections of tumour were reported by one consultant pathologist as well, moderately or poorly differentiated. The tumour was classified by its least differentiated area.

Dukes' classification

Tumour specimens were assessed by one pathologist in each case.

Specimen selection

In order to assess intratumour variability of the DNA profile and proliferation indices, multiple 1·0 cm wedges of tumour were excised from the peripheral quadrants and the centre of 62 tumours (*Table 1*). Sufficient tumour was excised in each wedge to allow for multiple analyses. All specimens were stored in 70 per cent ethanol at −4°C. Preservation of BRdUrd content for flow cytometry evaluation persists for at least 1 year using this method.

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Table 1 *Multiple tissue blocks were studied from 62 tumours. Up to six specimens were studied per tumour, as shown*

Number of specimens	Colon	Rectum
1	17	21
2	12	13
3	6	6
4	7	4
5	5	4
6	2	3

Tumour processing and BRdUrd staining for flow cytometry

Nuclear extraction. Specimens were minced and incubated in 8 ml porcine pepsin (Sigma Chemical Company, Poole, UK) solution in 0·1 M hydrochloric acid (0·4 mg/ml) for 45 min at 37°C while undergoing agitation. The resulting suspension was filtered through a 35 μm mesh and centrifuged at 1500 r.p.m. for 5 min to sediment the nuclei.

DNA denaturation. Nuclei were resuspended in 3 ml 2 M HCl for 13 min at room temperature to partially denature the DNA. Nuclei were then washed twice in fresh phosphate buffered saline (PBS). The concentration of nuclei was adjusted to approximately 2 million/ml.

Incubation with anti-BRdUrd monoclonal antibody. Nuclei were resuspended in a solution of 0·5 ml of PBS containing 0·5 per cent normal goat serum (NGS), 0·5 per cent Tween 20 (Sigma Chemical Company) and 25 μl of anti-BRdUrd antibody supernatant (ICRF, Sutton, UK) for 1 h at room temperature. Nuclei were then washed twice in PBS.

Staining with goat anti-rat antibody-FITC conjugate. Nuclei were resuspended in 0·5 ml 0·5 per cent Tween/NGS/PBS and 25 μl of goat anti-rat IgG (whole molecule)-fluorscein (FITC) conjugate (Sigma Chemical Company) for 1 h at room temperature. Nuclei were then spun and washed twice in PBS.

DNA counterstaining with propidium iodide. Nuclei were resuspended in 2 ml PBS containing 20 μg/ml of propidium iodide (Sigma Chemical Company).

Data collection and analysis by flow cytometry

The method of data analysis has previously been described by Wilson *et al.*[22]. Analyses were carried out on an Ortho Systems 50-H Cytofluorograph (Becton-Dickinson, Oxford, UK) with light excitation of 488 nm from a 5 W argon ion laser operating at 200 mW. Green fluorescent light (FITC) was collected at 510–560 nm and red fluorescence (PI) above 620 nm. All data were collected by the computer in list mode. The data were gated to exclude multiple nuclei on the DNA peak *versus* area signal. Data for 10000 to 15000 nuclei were collected from each specimen. The machine was calibrated before each batch analysis using fluorescent beads. The red gain was adjusted so that the G_1 diploid peak was situated near channel 200, with a tetraploid (G_2 diploid) peak around channel 400. Normal human colorectal mucosa specimens, which were always diploid, were used as internal controls in each batch. The exceptions were the few tetraploid tumours, in which case the G_1 diploid peak was set below channel 200, so that the aneuploid G_1 and G_2 peaks did not extend beyond channel 800. Using ethanol fixed material, complex multipeak profiles were rare and ploidy analysis using special software algorithms was not necessary. Mathematical analysis was performed according to the method of Begg. In this model the relationship of the T_{pot}, T_s and LI (total or aneuploid) is governed by the simple formula $T_{pot} = (T_s/LI) \times 0·8$, where 0·8 is the arbitrary value assigned to λ, a factor to account for population ageing[18,23]. The T_s and LI may vary independently.

Immunohistochemical localization of BRdUrd

BRdUrd labelling was studied in wax embedded tissue sections using the indirect avidin biotin peroxidase immunohistochemical technique[24]. An example of a stained tumour section is shown in *Figure 1*.

Results

A total of 100 adenocarcinomas of the colon and rectum were studied from 97 patients (54 men and 43 women, age range 42–90 years, mean age 74 years). Three female patients had two synchronous colonic tumours, each of which was studied. There were 49 colonic tumours and 51 rectal tumours. Of the tumours 23 were located in the caecum and ascending colon, four were in the transverse colon, nine were in the left colon, and 13 tumours were in the sigmoid colon. Five tumours were well differentiated, 65 were moderately differentiated and 30 were poorly differentiated. In three cases, endoanal surgery was performed and the Dukes' classification could not be assessed. Six patients had Dukes' A tumours, 39 patients had Dukes' B tumours, and 52 patients had Dukes' C tumours.

BRdUrd labelling was measured satisfactorily in at least one tissue block from every tumour (*Table 1*). The DNA histograms were unsatisfactory for measurement of the T_s and the T_{pot} in only two tumours for reasons which were unclear. Typical histograms obtained from diploid and aneuploid tumours are shown in *Figure 2*. In each example, the majority of labelled nuclei are still in the S phase of the cycle, between the G_1 diploid and aneuploid and the G_2 peaks, but some have already passed through G_2M. Their label has reappeared in the G_1 diploid and aneuploid populations of the next cell cycle. This label is clearly seen in the G_1 peaks on the left side of each BRdUrd histogram.

The mean DNA content and the number of labelled and

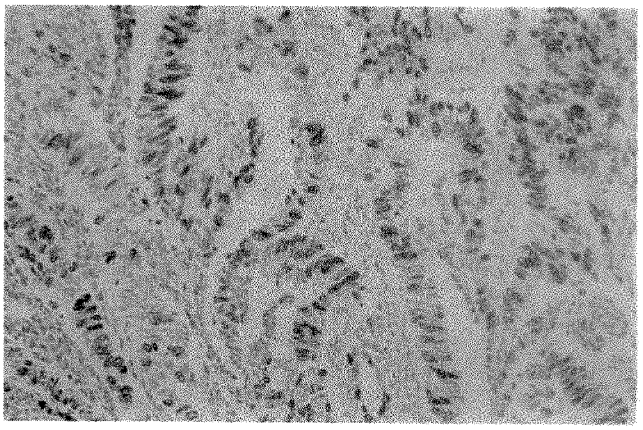

Figure 1 *A peroxidase stained section of a moderately differentiated colonic carcinoma (magnification* × *38)*

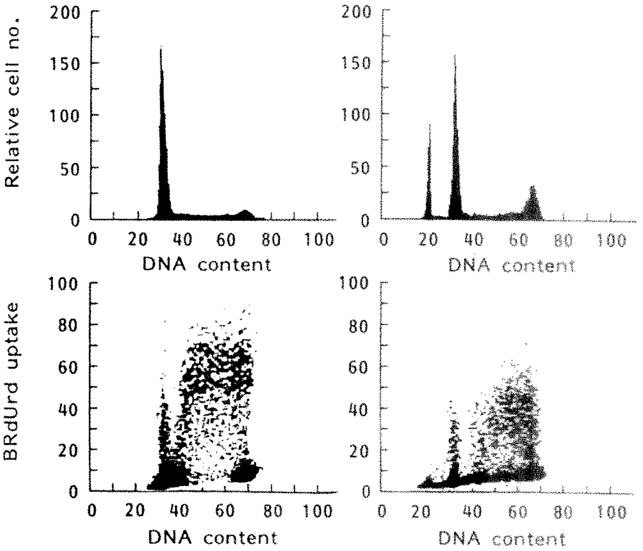

Figure 2 *Representative histograms of a diploid (left) and aneuploid (right) tumour are shown. The upper histograms are DNA profiles (PI staining). The lower histograms display the bromodeoxyuridine labelling in relation to DNA content. Each point represents one nucleus. Each tumour has been labelled 5–6 h before excision. The majority of labelled nuclei are still passing through S and G_2M, but some label has appeared in the G_1 phases of the next generation of cells*

Table 2 *Summary of the range of data measured in this series by multiparameter flow cytometry. The ploidy data are excluded from this table*

Parameter	Mean(s.e.m.)	Median	Range
Total labelling index (%, 100 primary tumours)	9·0 (0·5)	9·0	0·7–22·2
Total labelling index (%, 48 diploid tumours)	8·5 (0·6)	9·1	0·7–19·4
Aneuploid labelling index (%, 52 tumours)	12·1 (0·8)	12·0	2·0–25·5
T_s (hours)			
98 tumours	14·1 (0·5)	13·1	4·0–28·6
47 diploid tumours	11·6 (0·6)	11·1	4·0–20·5
51 aneuploid tumours	16·3 (0·8)	15·0	5·5–28·6
T_{pot} (days)			
98 tumours	5·9 (0·4)	3·9	1·7–21·4
47 diploid tumours	7·1 (0·8)	5·4	1·7–21·4
51 aneuploid tumours	4·8 (0·4)	3·5	1·9–15·4

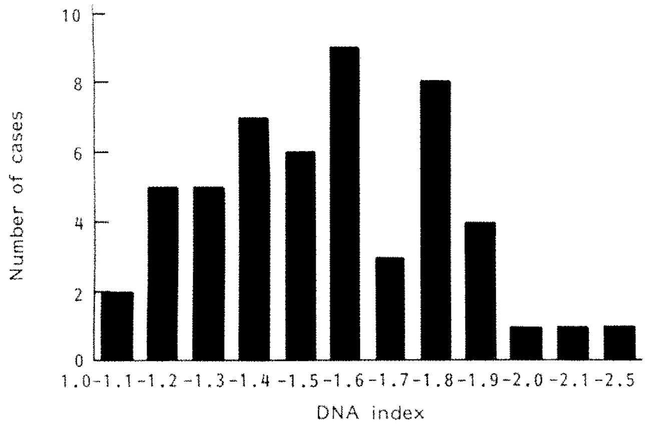

Figure 3 *The distribution of the DNA indices of 52 aneuploid colorectal carcinomas. There were 48 diploid tumours, DNA index = 1·0, which are omitted from this histogram*

unlabelled nuclei in any region of interest on the histograms is calculated by setting a gate. In the case of diploid histograms, gates are set around the total labelled population of nuclei to derive the labelling index, and around the BRdUrd labelled nuclei in G_1. These cells have divided and shared their BRdUrd between two daughter cells in the time between injection and biopsy. The labelling index can be corrected to its true value at the time of injection by halving the number of labelled nuclei in G_1 and subtracting it from the total labelled population. Regions are set around the total G_1, total G_2 and labelled S phase nuclei to measure the relative movement of S phase cells through the cell cycle in the period between injection and biopsy, assuming an even distribution of label through the S phase at time T_0. In the case of aneuploid BRdUrd histograms, both total and aneuploid labelling indices can be calculated by setting further regions according to DNA content. T_s and T_{pot} calculations are made on the aneuploid population, thus excluding labelled stromal nuclei.

The total and aneuploid labelling indices, T_s and T_{pot} results are given in *Table 2*. Where more than one biopsy was analysed the results given are the aggregated means of all data for that tumour.

DNA profile

Of the 100 tumours 52 were aneuploid (range 1·1–2·4). A histogram of the range of ploidy values is shown in *Figure 3*. Where multiple blocks were studied, 30 tumours showed diploidy in all blocks. In nine tumours, diploid and aneuploid populations were detected in different blocks. The variation in the interspecimen range of the DNA index of tumours from which multiple biopsies were analysed is shown in *Figure 4*.

Total and aneuploid labelling indices

The mean total labelling index of 100 tumours was 9·0 per cent (range 0·7–22·2 per cent, median 9·0 per cent). The mean aneuploid labelling index of 52 tumours was 12·0 per cent, (range 2·0–25·5 per cent, median 12·6 per cent) (*Figure 5*). A significant difference existed between the total and the aneuploid labelling indices when tested by both parametric and non-parametric methods (Student's *t* test, Mann–Whitney *U* test, $P = 0·01$). This is to be expected, because calculation of the total LI is based both on tumour nuclei and stromal nuclei, whereas the aneuploid population is composed entirely of tumour nuclei. This difference also existed between the total LI and the aneuploid LI of aneuploid tumours. There was no difference between the total labelling index of 48 diploid and 52 aneuploid tumours, suggesting that the proportions of non-proliferating cells in each type of tumour are similar. Because the aneuploid LI in those tumours with abnormal stem lines was on average 25 per cent greater than the total LI of those tumours, the data provide an indication of the underestimate of tumour cell proliferation in diploid tumours owing to the inability of flow cytometry to discriminate tumour and stromal nuclei[23]. Unlabelled stromal nuclei will produce an artificially low tumour labelling index in the diploid population. In aneuploid tumours, the proportion of tumour

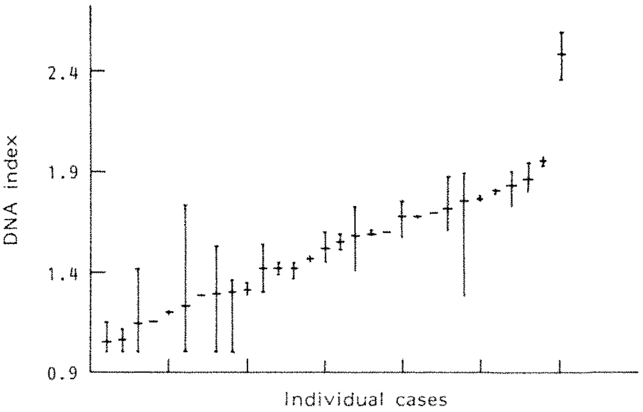

Figure 4 *The interspecimen variation in the DNA index of 30 aneuploid tumours from which multiple biopsies were studied. For each tumour the mean value and the range of values are plotted, in ascending order of the mean values*

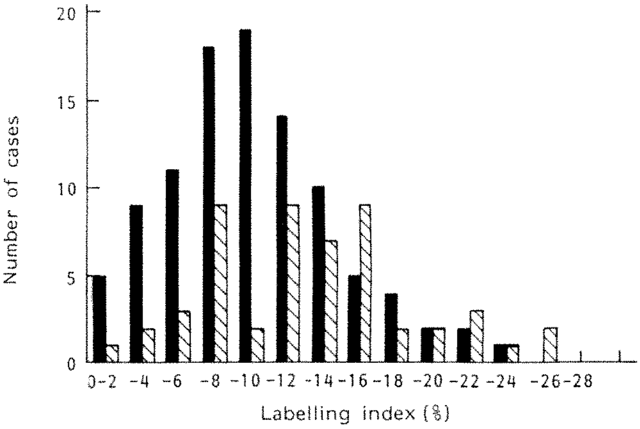

Figure 5 *The histogram shows the distribution of the total labelling index of 100 tumours* (■) *and separately of the aneuploid LI of 52 tumours* (▨), *plotted at 2·0 per cent intervals on the X axis. For tumours where multiple specimens were analysed the mean value was plotted (see text)*

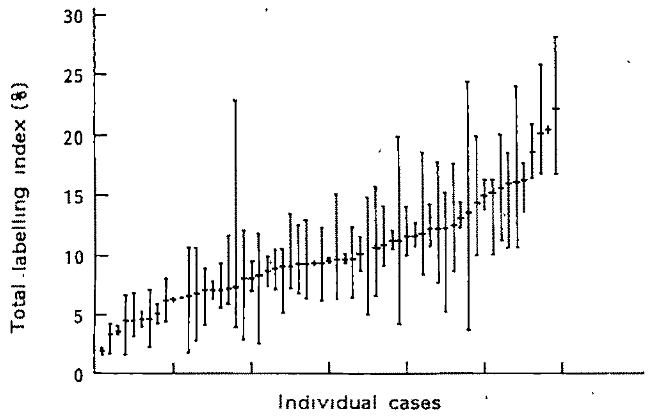

Figure 6 *The interspecimen variation in the total labelling index of 59 tumours from which multiple biopsies were studied. For each tumour the mean value and the range of values are plotted, in ascending order of the mean values*

Table 3 *The range of data obtained by measuring six adjacent biopsies from each of six randomly selected tumours*

Patient data	Mean(s.e.m.)	Range
No. 1, DI = 1·0		
Total LI%	6·3(1·3)	2·4–10·7
T_s (hours)	9·5(0·7)	9·2–11·3
T_{pot} (days)	5·9(1·0)	3·9–10·2
No. 2, DI = 1·53*		
Total LI%	12·6(1·3)	9·5–16·0
T_s (hours)	14·6(0·9)	8·0–13·1
T_{pot} (days)	3·5(0·3)	2·7–4·2
No. 3, DI = 1·50*		
Total LI%	13·3(0·8)	10·5–14·7
T_s (hours)	11·1(0·8)	8·0–13·1
T_{pot} (days)	2·9(0·3)	1·8–3·7
No. 4, DI = 1·0*		
Total LI%	11·8(1·0)	9·5–14·5
T_s (hours)	14·3(0·9)	11·6–16·8
T_{pot} (days)	3·8(0·2)	3·0–4·3
No. 5, DI = 1·41		
Total LI%	10·9(0·6)	9·0–12·8
T_s (hours)	17·2(0·6)	14·9–18·9
T_{pot} (days)	5·3(0·1)	4·9–5·6
No. 6, DI = 1·35*		
Total LI%	21·6(2·1)	15·7–26·7
T_s (hours)	21·6(3·7)	13·1–35·1
T_{pot} (days)	3·4(0·7)	1·4–5·2

LI%, labelling index, DI, DNA index; * one specimen not analysable: T_s, duration of the S phase, T_{pot}, potential doubling time

cells in the aneuploid and diploid populations is measured by the percentage of hyperdiploid cells in the population. (This includes some 'diploid' cells in S and G_2M). In our series, this ranged from 43–90 per cent. In tumours with a high fraction of diploid cells, it is likely that a significant proportion of the diploid cells are malignant rather than stromal.

In order to study intratumour heterogeneity between quadrants and between peripheral and central sites within the tumour, the total LIs of multiple blocks were compared in 60 tumours. Intratumour variation of the total LI ranged from 0–20 per cent, reflecting heterogeneity of proliferation (*Figure 6*).

Local heterogeneity was also studied in six immediately adjacent samples excised from each of six randomly chosen tumour blocks. Results are shown in *Table 3*. In two of the blocks there was a wide variation in data obtained, but in each case this derived from only one of five specimens. This may give an indication both of the range of experimental error and of the reproducibility in the method.

S phase duration and potential doubling time

The mean S phase duration of 98 evaluable tumours was 14·1 h (range 4·0–28·6 h, median 13·1 h) with a univariate distribution. A significantly longer T_s existed in the aneuploid tumours (two sample analysis of variance, $P = 0·001$) which could reflect the longer time required to duplicate the larger quantity of DNA in these tumours (*Figure 7*). Interspecimen variation in the T_s occurred within tumours (*Figure 8*). This may reflect in part a variation in the proportions of different cell lines in different specimens and also variation within any one cell line. The mean potential doubling time was 5·9 days (range 1·75–21·4 days, median 3·9 days) with a univariate distribution. The T_{pot} of aneuploid tumours was significantly shorter than that of diploid tumours, 3·5 *versus* 5·4 days, two sample analysis of variance, $P = 0·001$ (*Figure 9*) despite a longer T_s in aneuploid tumours. This reflects the higher labelling index in the aneuploid population used to calculate the T_{pot} in these tumours.

Where multiple blocks were studied, intratumour variation of the T_{pot} (*Figure 10*) reflected the heterogeneity of the total labelling index and of the T_s. Of 58 tumours 40 had a range of variation of the T_{pot} of less than 5 days, but seven tumours had a range of variation of greater than 10 days. Thus, reliance on a single biopsy to calculate the T_{pot} would result in misclassification of a significant number of tumours as rapidly or slowly proliferating.

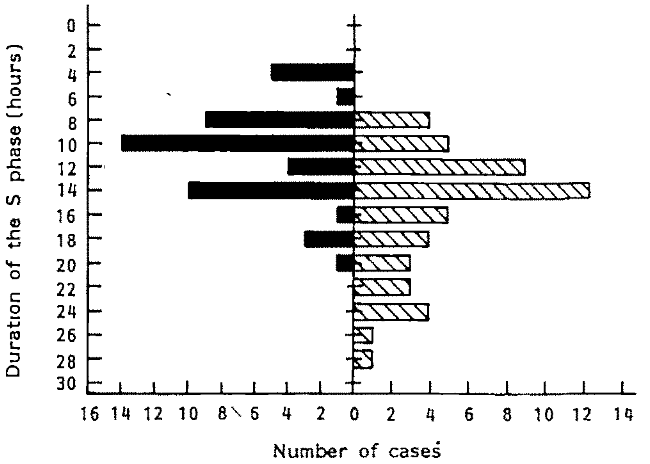

Figure 7 *Histograms plotted to compare the duration of the S phase of 47 diploid (■) and 51 aneuploid (■) tumours for which data were available. The duration of the S phase,* T_s, *of aneuploid tumours is significantly longer (see text)*

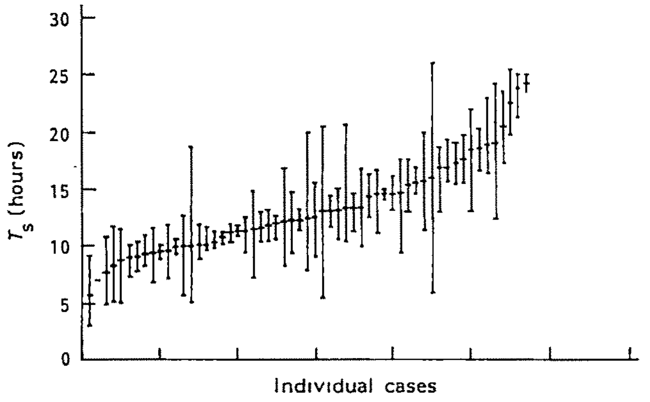

Figure 8 *The interspecimen variation in the S phase duration of 57 tumours from which multiple biopsies were studied. For each tumour the mean value and the range of values are plotted, in ascending order of the mean values*

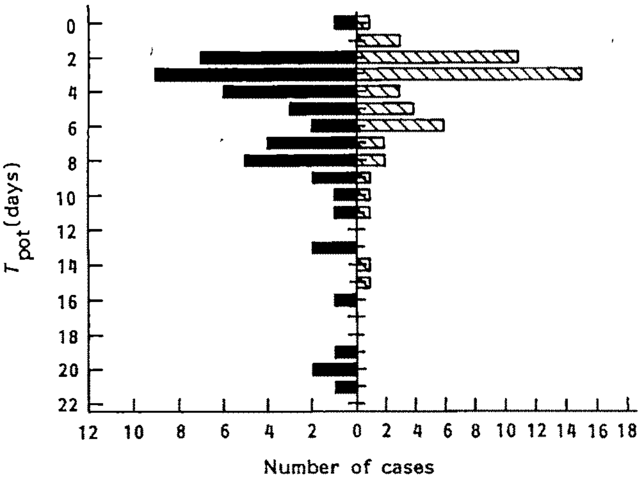

Figure 9 *Histograms plotted to compare the potential doubling time of 47 diploid (■) and 51 aneuploid (■) tumours for which data were available. The* T_{pot} *of aneuploid tumours is significantly shorter (see text)*

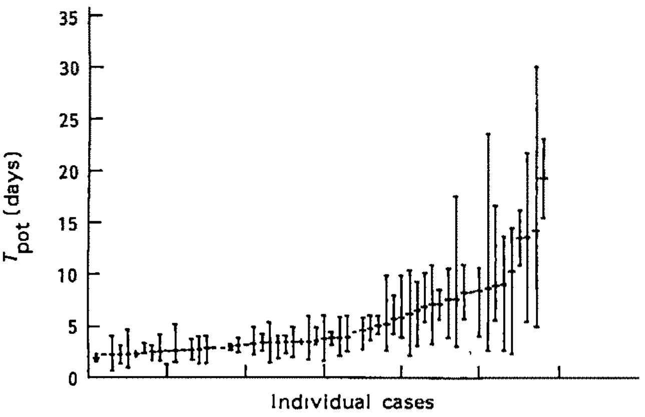

Figure 10 *The interspecimen variation in the* T_{pot} *in 58 tumours from which multiple biopsies were studied. For each tumour the mean value and the range of values are plotted, in ascending order of the mean values*

Relationship of ploidy to site of origin in the colon

It has been reported that the site of origin of a tumour[25] within the colon may affect its ploidy and kinetic characteristics. The 49 colonic tumours were grouped into 26 proximal (right + transverse colon) and 23 distal (left + sigmoid colon) categories. In the proximal group there were 18 diploid and eight aneuploid (ploidy range 1·12–2·0) tumours. In the distal group there were ten diploid and 13 aneuploid (ploidy range 1·14–2·49) tumours. The significance of this trend towards aneuploidy in distal tumours is unclear. There was no significant difference in total LI, T_s or T_{pot} between the two groups.

Kinetics of extraintestinal metastases

Four hepatic and two other metastases were studied in association with five primary tumours. No pattern of correlation was seen between the data from primary and metastatic lesions. A further ten specimens of recurrent tumour in the perineum, inguinal lymph nodes or subcutaneous deposits were studied. Kinetic data on the primary tumours were not available. Eight specimens were diploid and two were aneuploid, values 1·53 and 1·60. The mean labelling index was 10·2 per cent (range 2·5–17·3 per cent). The mean T_s (eight specimens) was 22·1 h (range 9·6–30·7 h). The mean T_{pot} was 8·9 days (range 2·6–28·9 days).

Correlation of results with current prognostic indicators

There was no relationship between the total labelling index and the histological grade or the Dukes' classification (*Figure 11*) (Student's *t* test, Mann–Whitney *U* test). There were too few well differentiated tumours for statistical significance. This lack of correlation with the histological grade was also found for the aneuploid LI and the DNA index of the aneuploid tumours, the T_s of all tumours. A similar lack of correlation was found between the T_{pot} and the histological grade or Dukes' classification (*Figure 12*).

Clinical safety of BRdUrd

At the time of injection, no acute events such as nausea, vomiting or anaphylaxis were reported or observed. The full blood count (particularly platelet count and white cell count) and renal function were monitored after surgery. There were no abnormalities in any of these parameters which could be attributed to BRdUrd. There were two deep venous thromboses in elderly patients. Each of the three early postoperative deaths was fully explained by the course of clinical events and the previous health of the patient. Post mortems were performed to confirm the cause of death wherever the consent of relatives was obtained.

Discussion

This paper describes the *in vivo* measurement of the static and dynamic cell kinetics of human colorectal tumours. All

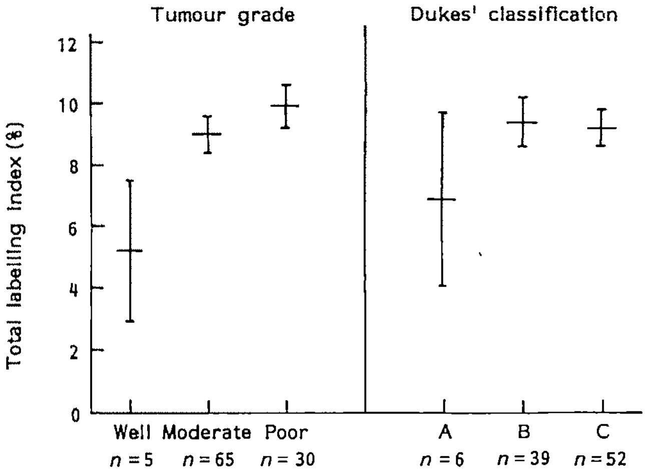

Figure 11 *The relationship of the total labelling index of 100 colorectal tumours to the histological grade and the Dukes' classification. The mean values and the error bars of the standard error of the mean are plotted (see text)*

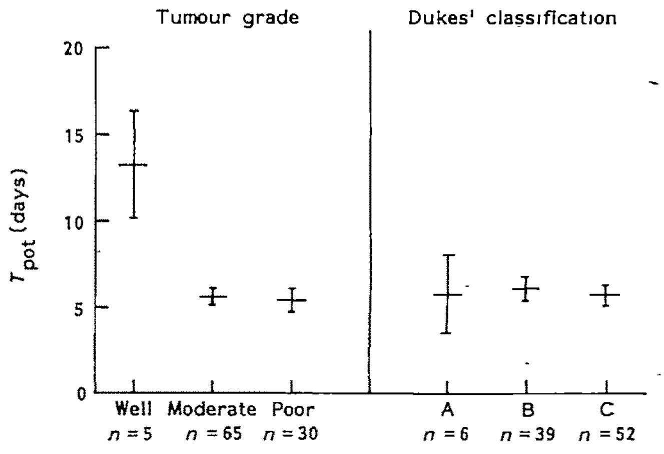

Figure 12 *The relationship of the potential doubling time of 98 colorectal tumours to the histological grade and the Dukes' classification. The mean values and the error bars of the standard error of the mean are plotted (see text)*

characteristics show both interpatient and intratumour variation. Sources of error in the method have been discussed elsewhere[22]. We have studied the heterogeneity of proliferation in single biopsies and tumours. The calculations assume that the BRdUrd bolus behaves as a true pulse label. This may not be true at the cellular level For example, BRdUrd delivery to the nucleus will be in competition with endogenous thymidine There may be failure to identify all S phase cells Disaggregation of tissues into nuclei is an empirical and tissue specific technique. We have found that colorectal tumour digestion is satisfactory in 0·4 mg/ml pepsin in 0·1 M HCl at 37°C for 40 min. One tumour showed marked disruption of the DNA profile in these and milder conditions. It is assumed that pepsin digestion shows no specificity for epithelial or stromal cells, so that the nuclear suspension contains representative fractions of nuclei from all cell types. It is not possible to confirm this by microscopy after cell digestion. Labelling of non-epithelial cells with BRdUrd, particularly lymphocytes, can be demonstrated histochemically but it is not possible to distinguish tumour from stromal nuclei in the diploid histogram. The contribution of labelled non-tumour nuclei in any profile cannot be known with precision, but histochemical staining indicates this figure to be 5 per cent or less in most specimens. Where available, the aneuploid profile of tumours is used to calculate the T_s and T_{pot}, because this profile is composed entirely of tumour cells The setting of gates on the BRdUrd histogram may introduce an observer error of up to 5 per cent. In particular, the late S phase merges with the G_2/M phase labelled nuclei, which may lead to overestimation of the mean DNA content of the labelled cells in the S phase.

The flow cytometry/BRdUrd method has significant advantages over previous methods used to study cell kinetics It avoids the need for radioisotopes and for serial biopsies in clinical practice. The complementary study of BRdUrd expression which is possible by flow cytometry and histochemical methods is a further advantage. The flow cytometer counts large numbers of nuclei with great accuracy. Multiple parameters can be measured simultaneously and ploidy analysis is obtained for all specimens. *In vivo* labelling with BRdUrd has physiological advantages over *in vitro* labelling, because the S phase label is delivered by blood flow rather than by diffusion into tissue blocks The entire analytical process has a potential turn-round time of one working day. This provides for the development of treatment strategies based on individual patient data.

Our labelling index data are broadly comparable with those obtained by *in vivo* and *in vitro* ^{3}H-thymidine and BRdUrd labelling of sections[4–7,26], despite the disruptive effect of the disaggregation procedure. Multiparameter flow cytometry therefore appears to offer little benefit in the measurement of a labelling index alone. Its value is in relating proliferation to the phases of the cell cycle. This reveals differential labelling of diploid and aneuploid populations. It allows the analysis of cell cycle progression. Time dependent data have been obtained by thymidine labelling of colorectal tumours in limited studies[26] and stathmokinetics[7]. For example, Lipkin in 1971 reported that the S phase duration of colorectal tumour cells was 10–20 h and the cell cycle time was 24–48 h[26]. Camplejohn[7] calculated a mean apparent cell cycle time T_{pot} of 190 h in 21 colorectal tumours using vincristine induced metaphase arrest *in vivo*. Our work therefore extends but also supports the findings of previous studies.

The volume doubling time (T_d) of human colorectal tumours measured by serial imaging has been estimated to range from 79 to 2355 days[27,28] If the T_{pot} data which we have presented are valid, then colorectal tumours have a much higher proliferative potential than is manifested in the observed growth rate There are several possible causes of this phenomenon The first is cell loss by exfoliation. Exfoliation of both viable and dead cells into the bowel lumen has been demonstrated[29–31]. Quantification of the rate of exfoliation of tumour cells is difficult *in vivo*. The second cause of cell loss is cell death by apoptosis and by necrosis. Central tumour necrosis is a prominent feature of many colorectal tumours, but is difficult to quantify A third possible but unquantified cause of cell loss is the failure of cell cycle progression by labelled cells Intratumour heterogeneity, both of mitotic activity[5] and of ploidy[8] is a feature of colorectal tumour growth. Biopsy specimens may not be representative of the whole tumour Aneuploid tumours may be derived from single or multiple stem cell lines, but stem cells cannot be identified by flow cytometry. The majority of aneuploid tumours showed little interspecimen variation of the DNA index, but in a few tumours ploidy varied from as much as 1 0 to 1·9 We have not observed hypoploidy. Flow cytometry is insufficiently sensitive to detect quantitative changes in DNA content in only one chromosome, and there will probably be an underestimate of the true aneuploidy incidence in any tumour population.

The DNA profile derived from specimens stored prospectively in ethanol is less affected by artefact than are the profiles derived from archival specimens. Failure to obtain an easily analysable DNA profile was rare in this series. DNA ploidy has been studied in human colorectal tumours as a determinant of prognosis[9–16,32–36] Jones *et al.*[16] concluded from a series of 123 human colonic tumours that DNA aneuploidy was associated with clinical and pathological features of aggressive malignancy, but that DNA ploidy was an incomplete measure of individual tumour behaviour We have not found any correlation between ploidy and histological grade or Dukes' classification in this series.

The relationship between tumour cell proliferation, DNA aneuploidy and biological aggressiveness is not yet understood Tubiana and Courdi[32] showed that the S phase fraction of breast carcinoma has the best correlation with clinical outcome. This may also be true of colorectal cancer, but we have demonstrated a wide intratumour variation in LI and T_{pot} data in approximately 10 per cent of our specimens, and would argue caution on any attempt to classify colorectal tumours for prognostic purposes as rapidly or slowly proliferating unless multiple specimens from multiple sites within the tumour have been measured. This is most practical using surgically resected specimens. We have shown that the labelling index alone is not a sufficient indicator of proliferation, because the T_s also varies within a tumour By combining the ploidy data, LI and T_s measurements to calculate the T_{pot}, the value of proliferation measurements as determinants of prognosis may be enhanced These will be reported when adequate follow-up has been achieved. We have not addressed the use of proliferation data in relation to adjuvant cytotoxic drug or radiotherapy scheduling in this paper. For example, knowledge of the S phase duration of rectal tumour cells may suggest the frequency with which radiotherapy fractions might be administered for optimum effect[37]. We believe that a sound knowledge of colorectal tumour cell kinetics derived from *in vivo* multiparameter measurement of proliferation may have an important role to play in research into better adjuvant therapies in clinical practice. This will be a most valuable goal

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Correlation between laboratory findings and clinical outcome after restorative proctocolectomy: serial studies in 20 patients with end-to-end pouch–anal anastomosis

Clinical function and anorectal physiological function were assessed and correlated in 20 patients with ulcerative colitis before restorative proctocolectomy and 3, 7, and 12 months after operation. The entire anal sphincter was preserved by means of a stapled pouch–anal anastomosis. Before operation, the median resting anal pressure was 79 cmH_2O (interquartile range 70–89 cmH_2O), the rectoanal inhibitory reflex was present in all patients and anorectal 'sampling' was noted in 16 of 20 patients. Three months after operation, resting anal pressure was 68 cmH_2O (range 50–87 cmH_2O) ($P<0{\cdot}001$), the reflex was present in only three patients ($P<0{\cdot}001$) and sampling was observed in one patient. After 7 months, resting anal pressure was 76 cmH_2O (range 64–89 cmH_2O), the reflex was present in 11 patients and sampling was observed in nine patients. At 12 months, resting anal pressure was 84 cmH_2O (range 66–94 cmH_2O), the reflex was present in 19 patients and sampling was observed in 17 patients. The compliance and capacity of the reservoir increased significantly. Ability to discriminate flatus from faeces was associated with return of the rectoanal reflex and sampling.

P. M. Sagar,
P. J. Holdsworth and
D. Johnston

University Department of Surgery,
The General Infirmary, Leeds
LS1 3EX, UK
Correspondence to.
Mr P. M Sagar

The paper by Martin *et al* in 1977 on the results of ileoanal anastomosis in children[1] and Parks and Nicholls' description in 1978 of the use of a pelvic ileal reservoir[2] led to renewed interest in restorative proctocolectomy. The operative technique used by Parks has undergone a number of modifications[3–5]. Abandonment of mucosal stripping and construction of a stapled, end-to-end anastomosis at the top of the anal canal have simplified the procedure and preserve the motor and sensory functions of the anal sphincter[6]

It is well recognized that when intestinal continuity is restored after restorative proctocolectomy bowel frequency is high initially but diminishes over a period of a few months. Our hypothesis was that adaptation of the reservoir and recovery of the anal sphincter occur during the first year after restorative proctocolectomy with preservation of the entire anal canal. Does the return of physiological function (rectoanal inhibitory reflex and 'sampling' episodes) correlate with the patient's ability to defer defaecation, discriminate accurately between flatus and faeces, and avoid minor leakage?

Patients and methods

Twenty patients were studied, nine men and 11 women of median age 31 years A triplicated ileal reservoir was constructed in eight patients and a quadruplicated reservoir in 12. The reservoir was anastomosed to the upper anal canal, 1–2 cm above the dentate line, by means of a stapled end-to-end anastomosis as described previously[6] Stripping of the anorectal mucosa was avoided to try to preserve anal sensation, the rectoanal inhibitory reflex[7] and sampling of rectal or reservoir content A defunctioning ileostomy was fashioned and closed 6–9 weeks later.

The following observations were made before operation and 3, 7 and 12 months after restorative proctocolectomy.

Anal manometry

Maximum resting anal pressure and maximum squeeze pressure were measured with the patient in the left lateral position by means of a closed, water-filled microballoon system with a diameter of 5 mm[6,8] The station pull-through technique was employed at 1 cm intervals

Anal sensation

Threshold electrosensitivity of the mucosa of the anal canal was measured in the upper, mid and lower anal canal (determined by anal manometry) by means of a bipolar constant current stimulator probe lubricated with a solution of KY Jelly® (Johnson and Johnson, Slough, UK) and normal saline in equal quantities[9]

Rectoanal inhibitory reflex

Presence or absence of the rectoanal inhibitory reflex was assessed by means of a latex balloon catheter, 10 cm in length, inserted into the rectum or reservoir The pressure in the anal canal was measured at the site of maximum resting anal pressure The balloon was inflated with air at a constant rate of 60 ml/min The reflex was said to be present if resting anal pressure decreased by more than 20 per cent in response to rectal or reservoir distension

Ambulatory manometry

These studies were carried out by means of a solid state pressure transducer catheter with a diameter of 2 mm (Gaeltec, Isle of Skye, UK)[10] This device incorporates two pressure sensors 5 cm apart The pressure recorded from each sensor was stored on a microchip in a portable electronic collecting system (Motility Digitrapper, Synectics Medical, Enfield, UK) for later computer analysis The distal pressure

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This paper was presented to a meeting of the Surgical Research Society held in Liverpool, UK, on 12 January 1990

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sensor, at the tip of the catheter, was in the rectum or reservoir and the proximal sensor was at the site of maximum resting anal pressure within the anal canal. The catheter was taped to the natal cleft and the digitrapper was secured with a belt around the patient's waist Patients were encouraged to undertake normal activities during the 3-h period of the recording

The recording was analysed for the presence of basal sphincter activity and for the occurrence of episodes of equalization of pressures within the reservoir and anal canal – so-called 'sampling episodes'.

Capacity and compliance of the reservoir

The capacity of the reservoir was determined by infusion of air at a constant rate of 60 ml/min into a latex balloon, 10 cm in length, attached to an 8 Fr catheter sited within the reservoir The maximum tolerated volume was the point at which the patient complained of pelvic discomfort or a strong urge to defaecate.

The compliance of the reservoir was determined by perfusion of a similar latex balloon with water at 37°C at a constant rate of 60 ml/min, pressure being measured by a water-filled manometer situated within the balloon. Compliance was taken to be the reciprocal of the slope of the resulting pressure–volume trace after correction for the characteristics of the balloon in air.

Clinical assessment of bowel function

The methods used were described previously[11,12].

Adequate discrimination was defined as the ability on the part of the patient not only to tell whether gas or faeces was present but also to pass flatus *per anum*, when socially acceptable, without any soiling or faecal leakage, and without having to visit the lavatory.

Urgency of defaecation was assessed by asking the patient for how long defaecation could be postponed after the need was first experienced Inability to wait for 15 min was arbitrarily taken to represent an unacceptable degree of urgency

Statistical analysis

All grouped data were expressed as medians and interquartile ranges. The groups were compared by means of the Wilcoxon matched-pairs signed-rank test for paired data and the χ^2 test[13].

Results

Anal manometry

Maximum resting anal pressure decreased from 79 cmH_2O (range 70–89 cmH_2O) before operation to 68 cmH_2O (range 50–87 cmH_2O) 3 months after operation ($P<0{\cdot}001$). This decrease was not maintained, however, because resting anal pressure returned to the level found before operation in 18 of the 20 patients during the subsequent 9 months (*Figure 1*).

Anal sensation

No significant change was found in the threshold electrosensitivity of the mucosa of the anal canal in its upper, middle or lower portions (*Figure 2*).

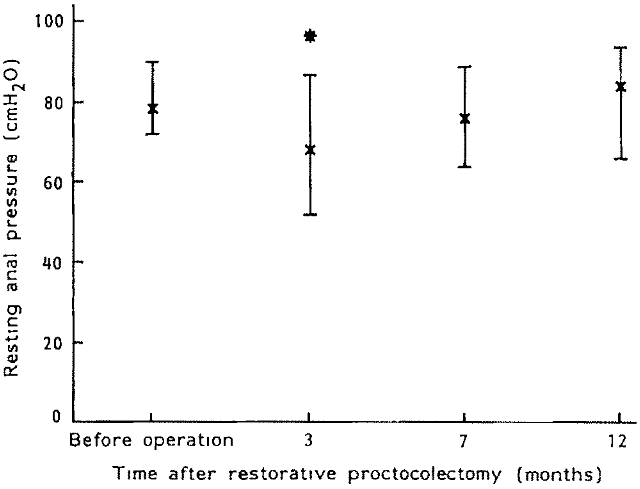

Figure 1 *Maximum resting anal pressure before and after operation. Resting pressure was reduced significantly 3 months after operation (* P<0·001) but had returned to normal by 12 months Medians and interquartile ranges are given*

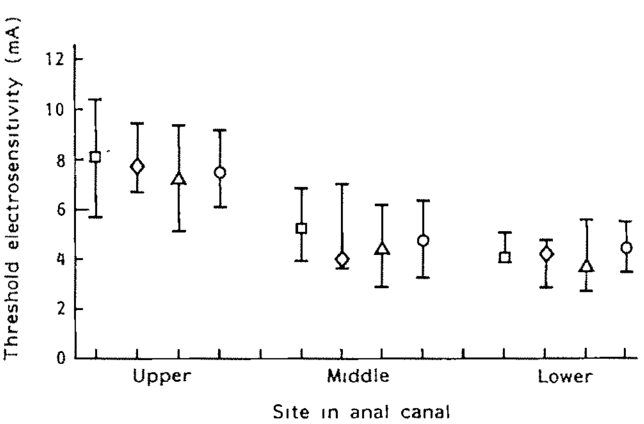

Figure 2 *Threshold electrosensitivity of the mucosa at different sites of the anal canal There was no significant change in threshold electrosensitivity at upper, middle and lower sites (as determined by prior anal manometry) over the 12-month period of the study Medians and interquartile ranges are given;* □, *before operation,* ◇, *3 months,* △, *7 months;* ○, *12 months after operation*

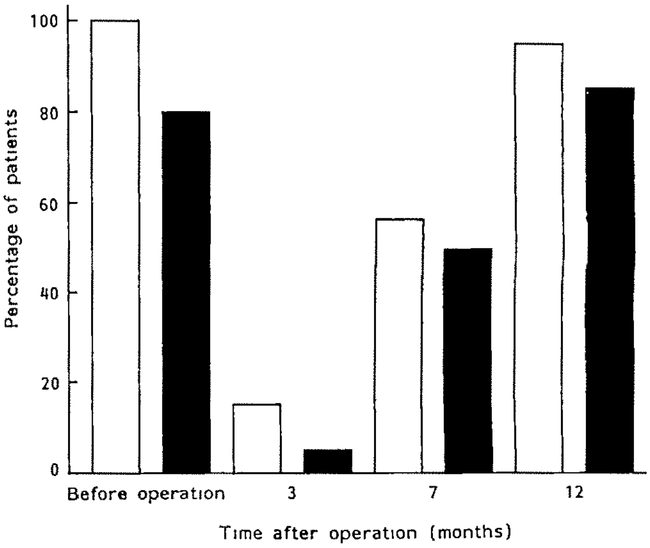

Figure 3 *Rectoanal inhibitory reflex* (□) *and sampling episodes* (■) *before and after operation. The reflex and equalization of pressures in the rectal or reservoir lumen and the anal canal (sampling) were lost in most patients 3 months after restorative proctocolectomy with a pelvic reservoir but had returned in most patients 12 months after operation*

Rectoanal inhibitory reflex

The rectoanal inhibitory reflex was present in each patient before operation but in only three patients 3 months after operation. The reflex was clearly demonstrable, however, in 11 patients 7 months after operation and in 19 of the 20 patients 12 months after operation (*Figure 3*)

Ambulatory manometry

Sampling episodes were observed in only one patient 3 months after operation, in nine of 20 patients 7 months after operation and in 17 of 20 patients 12 months after operation (*Figure 3*).

Correlation between discrimination, rectoanal inhibitory reflex and sampling

Three months after operation, two of the three patients with a demonstrable reflex, including the single patient who still had sampling episodes, were able to discriminate whereas only one of the 17 patients without the reflex could discriminate (n.s.).

Table 1 *Improvement in anorectal function among 20 patients studied for 1 year after restorative proctocolectomy with a pelvic reservoir and preservation of the entire anal canal*

	Time after operation (months)			
Clinical end-point	3	7	12	P*
Bowel frequency per 24 h	8 (7–9)	5 (4–6)	4 (3–5)	<0·001
Nocturnal bowel frequency	2 (2–3)	1 (0–1)	0 (0–1)	<0·001
Nocturnal soiling	6/20	3/20	2/20	n.s
Stool consistency loose	17/20	3/20	1/20	<0·001
Antidiarrhoeal medication	19/20	11/20	7/20	<0·01
Ability to defer defaecation for >15 min	2/20	15/20	19/20	<0·001
Ability to discriminate flatus from faeces	3/20	9/20	19/20	<0·001

Numbers in parentheses show ranges. * 3 *versus* 12 months

Seven months after operation, the inhibitory reflex was observed in 11 patients, of whom eight could discriminate flatus from faeces: in each of these eight patients, sampling episodes were also present. In contrast, of the nine patients in whom the rectoanal inhibitory reflex was still absent 7 months after operation, only one could discriminate satisfactorily ($P<0·05$) and in that patient sampling episodes were observed.

Compliance and capacity of the reservoir

The capacity (maximum tolerated volume) and the compliance of the reservoir increased with time after operation. The maximum tolerated volume increased from 190 ml (range 140–250 ml) at 3 months to 265 ml (range 175–350 ml) at 7 months ($P<0·001$) and to 290 ml (range 250–340 ml) at 12 months. Compliance increased from 9·1 ml/cmH_2O (range 7·2–10·0 ml/cmH_2O) at 3 months to 13·1 ml/cmH_2O (range 9·7–15·0 ml/cmH_2O) at 7 months ($P<0·001$) and to 13·7 ml/cmH_2O (range 11·6–14·8 ml/cmH_2O) 12 months after operation.

Functional results

The clinical results recorded in the 20 patients are shown in *Table 1*. Patients' need for antidiarrhoeal medication diminished and the consistency of the stool changed from loose to semisolid. None of the patients experienced incontinence or faecal leakage during the day, but faecal leakage at night was reported by six patients 3 months after operation and was still present in two patients 12 months after operation. The degree of leakage was, however, very slight by 12 months.

Only one patient was unable to defer defaecation for 15 min at 12 months: he had low reservoir compliance and suffered from recurrent attacks of 'pouchitis'.

Discussion

The principal findings were that significant adaptation of the pelvic reservoir and recovery of function in the anal sphincter took place during the 12-month period after restorative proctocolectomy with preservation of the entire anal canal. This was accompanied by a general improvement in the functional result. The return of the ano-'rectum' to normal physiological function correlated with the improvement in bowel function.

We have reported previously that resting anal pressure decreased significantly after restorative proctocolectomy[6,12,14]. When mucosal resection and a pull-through endoanal anastomosis were used, resting anal pressure decreased by about 50 per cent. Serial studies showed that this decrease was clinically important and that patients with the larger decreases in resting anal pressure experienced persistent faecal seepage or leakage[6,12,14,15]. In this study the resting anal pressure decreased significantly despite preservation of the entire anal canal and avoidance of mucosal stripping. This decrease, of about 10 per cent, was much less than the decrease recorded previously after mucosal resection and endoanal anastomosis. The decrease in resting anal pressure was transient and in 18 of the 20 patients resting pressure had returned to preoperative levels 12 months after operation. Williams, using a similar operative technique which eliminated the need for purse-string sutures[16], reported a much greater decrease in resting anal pressure, from a mean of 75 cmH_2O before operation to 34 cmH_2O after operation[17]. Such differences may result from variation in the extent of perimuscular rectal dissection, the diameter of the stapling device and the exact level of transection of the anorectum. Resting anal pressure is mainly a function of the internal anal sphincter. This sphincter may receive excitatory impulses from the rectal muscle wall and thus division of the anorectum at different levels could have different effects. The reduced resting anal pressure seen 3 months after operation may be due to the period of disuse during defunction and there may be an element of neuropraxis.

Electrosensitivity in the upper anal canal is blunted after mucosal proctectomy with an endoanal, ileoanal anastomosis, whereas after restorative proctocolectomy with an end-to-end anastomosis sensitivity in the anal canal is normal[18]. Preservation of the entire anal canal appears to prevent impairment of the sensory function of the sphincter as assessed by this technique and this is supported by the finding that most patients in this study had good discrimination 12 months after operation. In contrast, after mucosal proctectomy with an endoanal anastomosis, most patients felt that they could discriminate flatus from faeces, but fewer of them actually had the confidence to release flatus without fear of faecal leakage[6] Return of the ability to discriminate and to pass wind confidently in 19 of the 20 patients in this study coincided with the return of the rectoanal inhibitory reflex and sampling The rectoanal reflex is mediated by the intramural nerve plexus[19] and presumably the sampling episodes involve a similar mechanism. Regrowth of intramural nerves may occur across the anastomosis. This would account for the absence both of the reflex and of sampling episodes in the early period after operation Individual patients had a demonstrable reflex before the confidence to pass flatus returned. A psychological element may be involved as the patient adjusts from the preoperative state of urgency and frequency of bowel action to the satisfactory functional outcome after a successful restorative procedure.

The functional result of restorative proctocolectomy improves with time[20] and this is related to the compliance and capacity of the reservoir[12]: as the reservoir became more capacious and supple, so the functional result improved The changes in the maximum tolerated volume and the compliance of the reservoir were most marked between 3 and 7 months after operation. These findings are in accord with those of others[21,22]. It has been suggested that anorectal function does not stabilize until a year[23] or even longer[22] after operation

Serial studies carried out on 20 patients before and after restorative proctocolectomy with preservation of the entire anal sphincter showed that as the reservoir became more capacious and compliant, and as co-ordination between the reservoir and the anal sphincter returned, the clinical results improved The subtler forms of anal discrimination and the avoidance of minor faecal leaks were found to depend on return of the rectoanal inhibitory reflex and sampling episodes.

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Stools containing altered blood – plasma urea: creatinine ratio as a simple test for the source of bleeding

L. H. Olsen and K. H. Andreassen*

*Departments of Surgery, Sønderborg Hospital, and *Sundby Hospital, Denmark*

Correspondence to:
L. H. Olsen, parenkymkirurgisk afd., Sønderborg Sygehus, DK 6400 Sønderborg, Denmark

The plasma urea:creatinine ratio (U:C ratio) is known to be elevated in cases of upper gastrointestinal bleeding. Almost all patients with haematemesis have upper gastrointestinal (or generalized) bleeding so that in this study we characterized the diagnostic power of the U:C ratio in patients with stools containing altered blood without haematemesis in the hope that this simple laboratory test (used in conjunction, perhaps, with clinical data) might reduce the number of patients subjected to an unrewarding gastroscopy or colonoscopy. Of 76 cases seen in a provincial and a metropolitan hospital, 42 and 34 patients had upper and lower gastrointestinal bleeding, respectively. Fifty-four per cent of those with upper gastrointestinal bleeding and none of those with lower gastrointestinal bleeding had U:C ratios above 110 on admission. However, a discriminating level of 90 is considered to be more suitable, judged by the quadratic uncertainty score. At this level the odds for upper gastrointestinal bleeding were 15:1.

In patients with stools containing altered blood as the only sign of gastrointestinal haemorrhage the source of bleeding can be obscure because the colour of the stools depends not on the level of the bleeding source, but on the length of time the blood has remained within the intestinal lumen. A rational diagnostic strategy which could differentiate between upper and lower gastrointestinal bleeding may reduce the number of unnecessary and expensive procedures.

In 1933, Sanguinetti[1] reported an increasing plasma urea concentration in patients with gastrointestinal haemorrhage. The physiological basis for this observation is not fully understood and has aroused controversy[2–5]. In a retrospective study, Snook *et al.*[6] found that the plasma urea:creatinine ratio (U:C ratio) was significantly higher in patients with upper gastrointestinal bleeding than in patients with lower gastrointestinal bleeding. A high urea level caused by renal dysfunction or hypoperfusion is corrected by integrating plasma creatinine concentrations into the ratio. Snook *et al.* proposed that a U:C ratio above 100 indicates upper gastrointestinal bleeding, and a value below that level indicates lower gastrointestinal bleeding. Felber *et al.*[7] concluded, from a retrospective study in children, that a U:C ratio of 30 is discriminative. In these studies the U:C ratio was analysed in patients with both haematemesis and stools containing altered blood. Since almost all patients with haematemesis suffer from upper gastrointestinal bleeding, the diagnostic approach in these cases is obvious.

A prospective study has not yet been published on the accuracy of the plasma U:C ratio in discriminating upper from lower gastrointestinal bleeding in patients with stools containing altered blood. We have tried to find the optimal discriminating level for the U:C ratio.

Patients and methods

A total of 90 consecutive patients referred acutely to the surgical units of the Sønderborg and Sundby hospitals with a history of stools containing altered blood within the last 48 h, but without haematemesis, were studied. The former hospital is a county hospital in Jutland, the latter an urban hospital in the city of Copenhagen.

The final diagnosis was made by endoscopy, surgery, radiography or at autopsy. The U:C ratio was determined but not used to influence the diagnostic approach. Upper gastrointestinal bleeding was defined as a source of bleeding located proximal to the ligament of Treitz, and lower gastrointestinal bleeding as a bleeding source distal to this point. The description of stools is often inaccurate, especially when based on the patient's own inspection or the primary assessment on admission. The term stools containing altered blood was therefore used to describe any changes in stools implying gastrointestinal bleeding, this includes both melaena (black, tarry, sticky stools) and red stools.

Four patients were excluded, two because of previous admission in the study period, and two had diffuse bleeding from the gastrointestinal tract caused by essential thrombocytopenia and haemorrhagic diathesis. This was recognized in the primary blood samples. The source of bleeding was not found in 10 patients (*Table 1*). These patients all recovered spontaneously. None was readmitted with a bleeding episode or died after a mean observation period of 16·6 (range 9·9–23·0) months. They were not included in the analysis, leaving 76 patients for analysis.

Blood samples were taken on admission, after approximately 24, 48 and 72 h, and on discharge. Urea was analysed by an enzymatic method (mmol/l), and creatinine was analysed by a kinetic method (µmol/l). As an example, a blood urea of 5 mmol/l, and a creatinine value of 100 µmol/l would give a U:C ratio of 5×10^3 µmol/l:100 µmol/l; that is, 50. Both Departments of Clinical Chemistry used identical methods and there was no appreciable difference in their technical performance.

The Helsinki Declaration II was respected, and informed consent was obtained before the blood samples were taken; the study was approved by the local ethics committee.

Statistical analysis and calculations

Fisher's exact test and the Mann–Witney U test for unpaired data were used as appropriate. A 5 per cent level of probability (2α) was taken as significant.

A U:C ratio above the discriminating level, which is interpreted as a pointer to upper gastrointestinal bleeding, was taken to be a positive test result. The calculation of the predictive value of a positive test (PV_{pos}), the predictive value of a negative test (PV_{neg}), the sensitivity and the specificity are described elsewhere[8].

In the clinical situation the predictive values are most useful because they give the clinician a probability of disease (i.e. upper gastrointestinal bleeding) if the diagnostic test is positive.

The discriminating level for the U:C ratio was found by the quadratic scoring rule (Q) (equivalent to $0{\cdot}5Q_{30}$ in reference 9), which is a measure of diagnostic uncertainty. Q is determined using the

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Table 1 *Clinical data of 10 patients with an unknown bleeding source*

Patient no.	Age (years)	Urea:creatinine ratio	Diagnostic procedures	Haemaglobin level on admission (g/dl)	Number of blood units transfused
1	75	56	Proctoscopy, colon X-ray	13·2	0
2	86	150	Proctoscopy, colon X-ray	8·1	5
3	76	195	Proctoscopy, colon X-ray, gastroscopy	7·6	3
4	78	63	Gastroscopy, proctoscopy, colon X-ray	7·2	3
5	86	109	Gastroscopy	5·5	6
6	63	98	Gastroscopy, proctoscopy, colon X-ray	6·3	5
7	82	111	Gastroscopy, proctoscopy, colonoscopy	9·2	2
8	89	103	Gastroscopy, proctoscopy, ultrasound	8·5	2
9	88	28	None (refused)	13·4	0
10	76	109	Proctoscopy, laparotomy, proctoscopy	12·9	7

Table 2 *Clinical data of 76 patients with blood-altered stools*

	Bleeding source	
	Upper gastrointestinal tract ($n=42$)	Lower gastrointestinal tract ($n=34$)
Median age (range)	71·3 (38–96)	64·9 (20–85)†
Sex ratio (M:F)	1·8	1·3
Median haemoglobin level (g/dl) on admission (range)	9·5 (4–18)	13·0 (6–19)*
Median duration of blood-altered stools before admission (h; range)	19·5 (2–162)	18·0 (1–350)†
Diagnosis by		
Endoscopy	37	9
Radiology	0	20
Surgery	3	5
Autopsy	2	0

* $P<0·05$, † n.s.

Table 3 *Diagnoses of 76 patients with blood-altered stools*

Bleeding source			
Upper gastrointestinal tract ($n=42$)		Lower gastrointestinal tract ($n=34$)	
Gastric/duodenal ulcer	38	Colon diverticula	11
Haemorrhagic gastritis	2	Ulcerative colitis	4
Gastric carcinoma	1	Enterocolitis	4
Oesophagitis	1	Colon polyps	4
		Cancer of the colon and rectum	4
		Ileus of the small intestine	1
		Peutz–Jeghers syndrome	1
		Meckel's diverticulum	1
		Malignant lymphoma of the jejunum	1
		Proctitis	1
		Thrombosis of the superior mesenteric artery	1
		Bleeding vessel in the colon	1

following equation:

$$Q=\frac{1}{N}\left[\frac{n_{\text{pos}}^2}{n_{\text{pos}}-1}PV_{\text{pos}}(1-PV_{\text{pos}})+\frac{n_{\text{neg}}^2}{n_{\text{neg}}-1}PV_{\text{neg}}(1-PV_{\text{neg}})\right]$$

An ideal diagnostic test would score a Q value of zero.

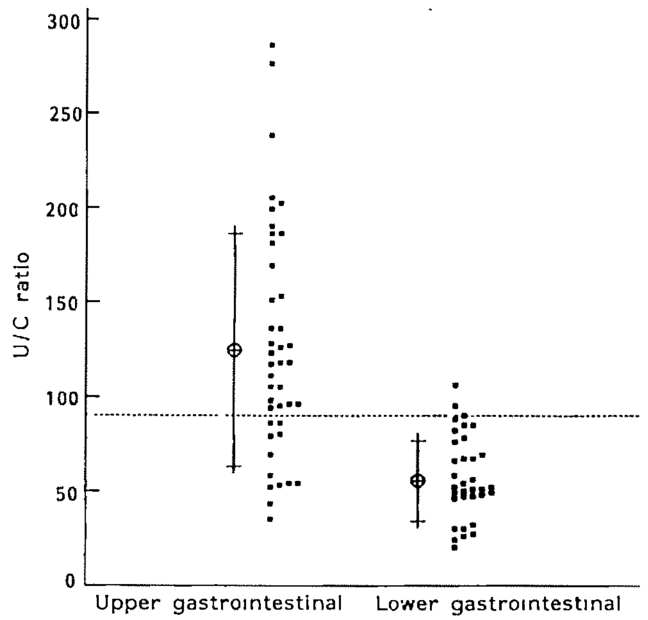

Figure 1 *Relationship between plasma urea:creatinine ratio (U:C ratio) and bleeding source* (P<0·001). *Bars show mean(s.d.) values*

Results

The clinical data of the 76 patients included in the study are shown in *Table 2*. A total of 42 patients had a bleeding source proximal to the ligament of Treitz, and 34 had a lesion distal to it The final diagnoses are listed in *Table 3*.

There were no differences in test performance or other descriptive data between the two centres.

The relation between plasma U:C ratio on admission and the source of haemorrhage is shown in *Figure 1*, and the distribution of patients for various classes of the U:C ratio is shown in *Figure 2*

The most suitable discriminating level was found to be a U:C ratio of 90, because the quadratic score ($Q=0·143$) was found to be lowest at this point, attaining 98 per cent of the estimated discriminatory ability of the test. The distribution of the patients at the chosen discriminating level, and its diagnostic and nosographic probabilities are shown in *Table 4*.

Theoretically, one would expect a decreasing U:C ratio in patients with a bleeding source in the upper gastrointestinal tract when bleeding stops. This proves to be correct as shown in *Figure 3*; the mean U:C ratios and their standard deviations during the first 72 h after admission are plotted for both groups of patients.

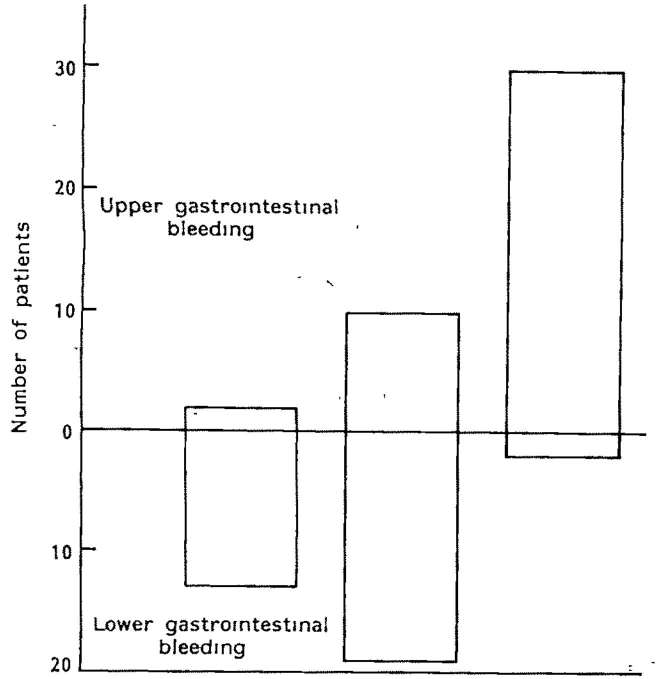

Figure 2 *Distribution of patients for various classes of the urea·creatinine ratio*

Table 4 *Distribution of patients for a discriminating level of 90 for the urea creatinine ratio* (P<0·01)

	Bleeding source	
Urea·creatinine	Upper gastrointestinal tract	Lower gastrointestinal tract
≥90	30	2
<90	12	32
Total	42	34

PV_{pos}, 0·94; PV_{neg}, 0·73; sensitivity, 0·71; specificity, 0·97

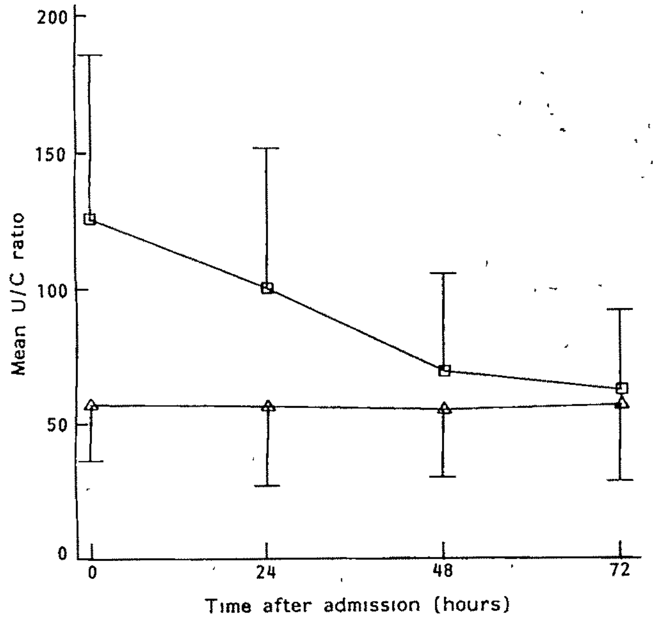

Figure 3 *Urea creatinine ratio during the first 72 h after admission. Values represent mean(s.d.).* □, *Upper gastrointestinal bleeding,* △, *lower gastrointestinal bleeding*

Discussion

In those patients hospitalized as emergency cases with stools containing altered blood, the clinician must decide between two different diagnostic strategies; namely, gastroscopy or proctoscopy with colon radiography/colonoscopy The choice is based on what is considered to be the most likely bleeding source at this point (the a priori probability). In this situation, a test performance with the highest number of 'true' test results is required. We propose a value of 90 as the only discriminating level for the U:C ratio: the odds for upper gastrointestinal bleeding above and below this level were 15:1 and 1:2·7, respectively. A higher discriminating level will cause too many patients to be examined for lower gastronintestinal bleeding.

The U:C ratio was ignored in the management of the bleeding episodes studied. In 32 patients the diagnostic approach started in the lower part of the gastrointestinal tract, although seven patients proved to have a lesion in the upper part of the tract. None of the latter had a U:C ratio below 90. However, the U:C ratio would have led to a wrong diagnostic approach, looking for upper gastrointestinal bleeding, in only two of the remaining 25 patients.

In contrast to other diagnostic tests, the U:C ratio is a measure which determines the diagnosis of two different 'diseases' (i.e. upper and lower gastrointestinal bleeding), whereas most tests determine only whether the patient has a disease or not. This makes the finding of the most suitable discriminating level more difficult. Do we wish to avoid overlooking upper gastrointestinal bleeding or lower gastrointestinal bleeding, and what are the consequences of delayed diagnosis?

The U:C ratio does not stand alone in the diagnostic approach to a patient with stools containing altered blood; however, it could be used as an early pointer in the management of these patients.

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Changes in anal canal sensation after childbirth

H. Cornes,
D. C. C. Bartolo* and
G. M. Stirrat

*University Departments of Obstetrics and *Surgery, Bristol Maternity Hospital and Bristol Royal Infirmary, Bristol, UK*
Correspondence to:
Miss H. Cornes, Department of Obstetrics, Arrowe Park Hospital, Arrowe Park Road, Upton, Wirral L49 5LN, UK

Obstetic trauma predisposes to faecal incontinence. Anal canal sensation is impaired in incontinent patients. To assess the effect of childbirth on anal canal sensation anal mucosal electrosensitivity was measured in 122 primiparous patients in the immediate postnatal period and in 74 at 6 months postpartum. There were 35 normal vaginal deliveries, 36 forceps deliveries, 20 ventouse extractions, ten vaginal breech deliveries and 21 caesarean sections. Sensation was impaired in the lower, mid and upper anal canal immediately after delivery in those patients who had a normal vaginal delivery or a forceps delivery when compared with controls or with those delivered by caesarean section. Women who had ventouse deliveries had impaired sensation immediately after delivery in the mid anal canal compared with controls and those undergoing caesarean section. By 6 months there were no differences between any group. Patients who sustained a division of the external anal sphincter at delivery had impaired sensation which persisted in the upper anal canal at 6 months.

Obstetric trauma is an important aetiological factor in the pathogenesis of faecal incontinence. This can be due to neuropathic damage, to a tear in the external anal sphincter or to a combination of these.

Patients with faecal incontinence have been shown to have reduced anal canal sensation which improves following successful reconstructive surgery[1,2].

The aim of this study was to determine the changes in anal canal sensation after childbirth and to assess the relationship to the mode of delivery.

Patients and methods

One hundred and twenty-two primiparous patients were studied at between 1 and 10 days postpartum (87 per cent between 2–6 days) from November 1988 until January 1990. The subjects were recruited from the postnatal wards to obtain a range of patients with different modes of delivery. To date 96 patients have been asked to attend for a 6-month follow-up appointment and, of these, 74 have attended, which represents a return rate of 77 per cent. The 22 patients who did not wish to complete the study were telephoned where possible and details of any symptoms were recorded. None of the patients was diabetic or had neurological disease. Sixteen patients were seen antenatally as controls.

A questionnaire was completed and details of bowel symptoms were recorded. The duration of labour and the type of delivery were documented, paying attention to details of any perineal trauma.

Mode of delivery

Thirty-five patients had a normal vaginal delivery. There were 36 forceps deliveries of which 30 were 'lift outs' and six were Kielland's rotational forceps deliveries. Twenty patients were delivered with the ventouse vacuum extractor and ten had a vaginal breech delivery. Twenty-one caesarean sections were performed of which 15 were in labour (six for failure to progress, seven for fetal distress and two for breech presentations) and six were performed electively.

The follow-up studies to date include 20 normal deliveries, 24 forceps, 13 ventouse, six vaginal breech deliveries and 11 caesarean sections.

Perineal trauma

In the spontaneous vaginal delivery group there were four patients with an intact perineum, four with a first degree tear, 13 with a second degree tear (three of which extended causing a tear in the external anal sphincter), 13 with an episiotomy (two of which extended causing a tear in the external anal sphincter) and one third degree tear.

All patients delivered with the obstetric forceps had an episiotomy and of these seven sustained a tear to the external anal sphincter.

In the group delivered with the ventouse vacuum extractor 19 patients had an episiotomy, one of which extended to a tear in the external anal sphincter, and one patient had a third degree perineal tear.

There were no torn sphincters in the vaginal breech delivery group but all these patients had an episiotomy performed.

All patients delivered by caesarean section had an intact perineum.

The study was approved by the ethical committee of the Bristol and Weston Health Authority and informed consent was obtained from each patient.

Anal manometry

Anal manometry was performed using a water-filled microballoon, 5 mm in diameter, connected via non-distensible tubing to a pressure sensing system (Hewlett Packard, Bracknell, UK) with output to a chart recorder (Devices, Welwyn Garden City, UK). Using a station pull-through technique the sphincter length, maximum pressure at rest and maximum pressure with a voluntary contraction were measured.

Anal mucosal electrosensitivity

Anal mucosal electrosensitivity was measured in the lower, mid and upper anal canal. A catheter with two platinum electrodes at its tip, 1 cm apart, was inserted into the anal canal and a small pulsed electric current was passed across the electrodes from a constant current generator (Department of Medical Physics, Bristol Royal Infirmary, Bristol, UK). The current was increased until the patient noticed a tingling feeling and this was taken as the threshold of anal sensation. Three readings were taken at each site and the mean value was recorded.

Statistical analysis

Results given are medians with ranges in parentheses. The Mann–Whitney *U* test was used to compare different groups.

Results

Symptoms

Twenty-one patients had some degree of faecal incontinence after childbirth. At 6 months, two patients were incontinent to solid stool and 13 patients were incontinent to flatus. In addition, four patients had one episode of incontinence to liquid stool during the first fortnight after delivery and two patients were incontinent to liquid stool on several occasions in the first 2 months after delivery. In all, by 6 months, 22 patients complained of urgency of defaecation dating from delivery

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Table 1 *Anorectal manometry*

Mode of delivery	Immediately postpartum: Maximum resting pressure (mmHg)	Immediately postpartum: Maximum voluntary contraction (mmHg)	6 months postnatal: Maximum resting pressure (mmHg)	6 months postnatal: Maximum voluntary contraction (mmHg)
Normal	50 (25–95)†§	65 (35–135)†§	68 (37–115)	121 (52–195)*‡
Forceps	50 (10–75)†§	60 (16–105)†§	65 (40–100)	102 (55–185)†§
Ventouse	50 (25–80)†§	72 (33–120)†§	60 (30–105)	98 (55–200)*‡
Breech	47 (30–70)*‡	70 (45–102)†§	68 (40–75)	124 (85–150)‡
Caesarean section	65 (45–115)	118 (85–218)	75 (55–100)	155 (110–245)
Controls	70 (50–90)	140 (115–200)		

Results are medians with ranges in parentheses; * $P<0{\cdot}05$ *versus* controls, † $P<0{\cdot}01$ *versus* controls, ‡ $P<0.05$ *versus* caesarian section, § $P<0{\cdot}01$ *versus* caesarian section

Table 2 *Patients with torn external anal sphincter*

	Torn external anal sphincter: Immediately postpartum ($n=15$)	Torn external anal sphincter: 6 months postpartum ($n=12$)	Controls
Sphincter length (cm)	2·0 (2–4)*	3·0 (2–4)	3·0 (2–4)
Maximum resting pressure (mmHg)	38 (25–65)†	60 (40–100)	70 50–90)
Maximum voluntary contraction (mmHg)	55 (33–105)†	90 (55–125)†	140 (115–200)
Lower anal canal sensation (mA)	7·6 (2·6–13·5)*	4·9 (2·0–14·9)	4·4 (2·5–8·9)
Mid anal canal sensation (mA)	7·1 (3·3–14·8)†	5·0 (3·3–22·7)	4·1 (2·4–7·3)
Upper anal canal sensation (mA)	9·8 (2·6–26·0)*	7·7 (2·8–26·0)*	4·3 (1·8–10·0)

Results are medians with ranges in parentheses; * $P<0{\cdot}05$ *versus* controls; † $P<0{\cdot}01$ *versus* controls

Fourteen of the patients who sustained a tear to the external anal sphincter have been followed up at 6 months. This group included the two patients who were incontinent to solid stool and five of the patients who were incontinent to flatus. These seven patients also complained of urgency of defaecation.

Anal manometry

The maximum resting pressure was significantly lower in the immediate postnatal period in all patients who delivered vaginally when compared with those delivered by caesarean section or with the controls. By 6 months there was no difference in resting pressure between any of the groups (*Table 1*).

The pressure with a maximum voluntary contraction was significantly lower in the immediate postnatal period in all patients who delivered vaginally when compared with those delivered by caesarean section or with the controls. At 6 months all patients showed a significant improvement in their maximum voluntary contraction pressures ($P<0{\cdot}01$, Wilcoxon paired signed rank test) but the patients delivered vaginally still had significantly lower pressures when compared with women delivered by caesarean section or the controls (*Table 1*).

The group of patients with a torn external anal sphincter had a lower maximum resting pressure than controls immediately after delivery ($P<0{\cdot}01$) but no significant difference by 6 months. The maximum voluntary contraction pressures were significantly lower than controls both immediately after delivery ($P<0{\cdot}01$) and at 6 months ($P<0{\cdot}01$) (*Table 2*).

Anal mucosal electrosensitivity

Sensation in the lower anal canal was impaired after normal vaginal delivery and forceps delivery in the immediate postnatal

Table 3 *Anal mucosal electrosensitivity immediately postpartum*

Mode of delivery	Lower anal canal (mA)	Mid anal canal (mA)	Upper anal canal (mA)
Normal	5·8 (2·1–13·5)*‡	5·7 (1·8–15·2)*‡	6·5 (2·4–26)*‡
Forceps	6·7 (2·8–12·3)†§	6·3 (3–26)†§	8·5 (3·3–26)†§¶
Ventouse	6·1 (2·1–13·6)	5·7 (2·4–12·3)*	5·5 (1·9–26)
Breech	5·0 (3·3–11·8)	4·4 (2·9–9·7)	5·6 (2·9–8·9)
Caesarean section	4·4 (3·3–9·3)	4·4 (2·4–7·6)	5·1 (2–12·4)
Controls	4·4(2·5–8·9)	4·1 (2·4–7·3)	4·3 (1·8–10)

Results are medians with ranges in parentheses; * $P<0{\cdot}05$ *versus* controls; † $P<0{\cdot}001$ *versus* controls; ‡ $P<0{\cdot}05$ *versus* caesarian section; § $P<0{\cdot}001$ *versus* caesarian section; ¶ $P<0{\cdot}05$ *versus* normal, ventouse and breech deliveries

Table 4 *Anal mucosal electrosensitivity 6 months postpartum*

Mode of delivery	Lower anal canal (mA)	Mid anal canal (mA)	Upper anal canal (mA)
Normal	4·7 (2·9–14·9)	4·5 (2·2–22·7)	4·9 (2·3–26·0)
Forceps	4·3 (2·0–9·6)	3·9 (2·2–8·3)	4·9 (2·1–23·0)
Ventouse	5·0 (2·8–7·3)	4·6 (2·3–8·7)	4·9 (2·2–12·2)
Breech	3·9 (2·5–6·6)	3·1 (2·2–10·0)	3·6 (2·2–12·3)
Caesarean section	3·6 (2·3–5·5)	3·5 (1·9–9·3)	3·6 (2–12·8)
Controls	4·4 (2·5–8·9)	4·1 (2·4–7·3)	4·3 (1·8–10·0)

Results are medians with ranges in parentheses; there were no significant differences period compared with caesarean sections and controls but by 6 months there were no significant differences (*Tables 3* and *4*).

The mid anal canal showed impaired sensation after normal, forceps and ventouse deliveries initially but no differences by 6 months.

In the upper anal canal there was impaired sensation after normal delivery compared with caesarean section and controls initially. The forceps group had impaired sensation compared with normal, ventouse, vaginal breech deliveries, caesarean sections and controls immediately after delivery but there were no significant differences between any of the groups at follow-up.

Sensation in the lower, mid and upper anal canal was impaired in the immediate postnatal period in the patients sustaining a tear in the external anal sphincter at delivery when compared with controls. This impairment persisted in the upper anal canal at 6 months but not in the lower or mid anal canal.

Discussion

The anal canal is richly innervated by sensory organs and free nerve endings and it has been shown that the anal epithelium is sensitive to pain, temperature, touch and movement[3,4]. Duthie and Bennett[5] demonstrated that the upper anal canal opens reflexly to allow intrarectal contents to come into contact with the sensory zone of the anal canal. They termed this the sampling response and suggested that this mechanism may allow sensation in the anal canal to play a part in the fine adjustment of anal continence. Miller *et al.* studied patients with faecal incontinence and found that they had defective anorectal sampling responses[6].

Anal sensation has been quantified using the technique of anal mucosal electrosensitivity. Roe *et al.*[7] found that patients with faecal incontinence had a sensory deficit in the anal canal while sensation in patients with anal fissures was more acute. This latter finding was attributed to exposure of nerve endings within the fissure. The reduced sensation in incontinent patients could be ascribed to mucosal prolapse or sensory nerve denervation. Rectal mucosa is considerably less sensitive than anal epithelium and patients with incontinence invariably have some element of prolapse of the anal lining. Reduced sensation may be due to poor contact between the stimulating probe and the anal lining because of low sphincter pressures.

The outcome following anterior sphincter plication and levatorplasty in the treatment of faecal incontinence was related to improved upper anal canal sensation after surgery[1] A similar improvement in anal canal sensation had previously been described following postanal repair for incontinence[2]. This reduction in sensory threshold is probably due to lax or prolapsed anal mucosa being drawn back up into the anal canal These studies[1,2,7] have shown that anal mucosal electrosensitivity is useful in the assessment of patients with faecal incontinence. Rogers *et al.*[8] also found that there was a sensory deficit of the anal canal in neuropathic faecal incontinence and that this occurred in combination with the motor neuropathy of the anal canal musculature. Rogers *et al.*[9] found that these tests were reproducible and consistent.

Obstetric trauma is known to be a predisposing factor in the development of faecal incontinence. Previous studies have shown that delivery can cause damage by direct injury to the anal sphincter, damage to the innervation of the pelvic floor musculature, or both these factors[10–12]. Such patients may not present until later because the early symptoms are mild, because of preoccupation with the newborn baby or because of the patient's embarrassment.

This study demonstrates that patients who have a vaginal delivery had a reduction in maximum resting pressure and maximum voluntary contraction pressure in the immediate postnatal period. The reduction in maximum resting pressure was small. This may reflect some internal anal sphincter damage but may be due to a reduction in the external sphincter component of the resting pressure (normally up to 30 per cent of resting pressure is due to the external anal sphincter)[13,14] By 6 months the resting pressure had returned to normal In contrast, the maximum voluntary contraction pressure remained lower than controls at 6 months and was most marked in those patients delivered with the obstetric forceps.

Sensation was impaired after normal and forceps deliveries at all levels of the anal canal immediately after delivery, but only in the mid anal canal after ventouse delivery. This impairment of sensation after delivery is probably due to a combination of mucosal prolapse and pudendal neuropathy.

Forceps may initially cause more damage than the ventouse vacuum extractor and increased use of the ventouse vacuum extractor over the obstetric forceps could reduce future problems due to obstetric trauma in those cases where either is appropriate from the obstetric point of view

Patients with a torn external anal sphincter still have sensory impairment in the upper anal canal at 6 months and 50 per cent of these have bowel symptoms. Patient embarrassment about the condition may prevent them from consulting a doctor, leaving the obstetrician unaware of these problems. Previous studies have documented the relationship between anorectal symptoms and sphincter disruption following delivery[15,16].

Patients who undergo primary sphincter repair in the immediate postpartum period have impaired sphincter function which may be sufficient to result in anorectal incontinence. Those who retain continence but have lowered anal canal pressures and impaired anal canal sensation may develop overt faecal incontinence subsequently.

These patients should be identified so that further 'traumatic deliveries' are avoided. Patients who sustain a tear to the external anal sphincter should be followed up closely and undergo electromyography, pudendal nerve latency studies, anal sensory measurements and anal manometry.

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Role of the protease–antiprotease balance in peritoneal exudate during acute pancreatitis

C. Wilson, A. Shenkin*
and C. Imrie

Departments of Surgery and
**Pathological Biochemistry, Royal*
Infirmary, Glasgow, UK
Correspondence to:
Mr C. Wilson, Division of Surgery,
Stobhill General Hospital, Glasgow
G21 3UW, UK

The peritoneal exudate formed during experimental pancreatitis is toxic when administered intraperitoneally or intravenously to other animals. Overwhelming of the peritoneal antiprotease defences by proteolytic enzymes released from the pancreas may be a key factor responsible for this toxicity and is examined in the current study. Human pancreatitis exudates possessed tryptic amidase activity indicating trypsinogen activation. The trypsin inhibitory capacities of exudates were reduced indicating a degree of consumption of the peritoneal antiproteases. Of 21 exudates examined, three showed marked reduction of their trypsin inhibitory capacity indicating almost complete consumption of their antiproteases. All three patients were shocked at the time of sampling, two dying of fulminant pancreatitis within 24 h. Overwhelming of the peritoneal antiproteases was not confirmed, but may occur in a few instances where proteolytic enzyme release or zymogen activation continues. Intraperitoneal administration of exogenous antiproteases prolongs survival in rats with pancreatitis and has been suggested as a therapy in man. The current data suggests that few patients are likely to benefit from such an approach.

The exudate formed during experimental pancreatitis has been shown to possess toxic properties when administered intraperitoneally or intravenously to other animals. These effects include hypotension[1–4], increased vascular permeability[5], haemoconcentration[6,7] and death[8–11]. The toxic factor (or factors) have not been fully characterized but may include pancreatic enzymes, complement breakdown products, kinins or other small vasoactive peptide molecules and prostaglandins. Overwhelming of the peritoneal antiprotease defences by proteolytic enzymes released from the pancreas may be a central factor in this toxicity[12–14].

The key protective antiprotease in the peritoneal exudate appears to be α_2-macroglobulin, preferentially binding activated proteolytic enzymes[13]. The complete consumption of α_2-macroglobulin during the course of pancreatitis in the dog coincides with the onset of irreversible shock from which the animals subsequently die[12,13]. Activated proteolytic enzymes have previously been demonstrated in the pancreatitis exudate in man, in complex with α_2-macroglobulin and α_1-antiprotease. High degrees of consumption of α_2-macroglobulin, up to 100 per cent, have been recorded[15,16] suggesting that this may be important in man as a possible explanation for the early systemic toxicity observed in severe attacks.

The aims of the present study were to investigate whether overwhelming of the peritoneal antiproteases occurs in human acute pancreatitis, to examine any clinical sequelae and ascertain whether these biochemical changes were unique to acute pancreatitis.

Patients and methods

Peritoneal exudate was obtained by paracentesis in 21 patients considered on clinical criteria to have a moderate or severe attack of acute pancreatitis[17] (corresponding to approximately 17 per cent of the total admitted with pancreatitis during the period studied). The patients were admitted a median of 9 h (range 1–36 h) from the onset of their attack and peritoneal cannulation was performed a median of 8 h after admission (range 4–31 h). Two groups of patients were compared, ten who died and 11 who survived their illness (*Table 1*)

Peritoneal exudate was also obtained at laparotomy in seven patients with a perforated peptic ulcer (duodenal – six, gastric – one), from eight patients with intestinal obstruction and from one patient with hyperamylasaemia due to extensive mesenteric venous infarction. Twelve further patients with a pancreatic pseudocyst had their cyst fluid sampled, ten at cystogastrostomy and by percutaneous drainage in two. The samples were centrifuged at 4°C and the supernatants separated and deep frozen, usually within 1 h of sampling, and stored at −20°C until assay.

Biochemical investigations

Total protein and albumin were measured by the biuret and bromcresol green methods respectively. Amylase (Phadebas test, Pharmacia Diagnostics, Uppsala, Sweden) and lipase activities (Lipase UV test kit, Boehringer Mannheim, Mannheim, Germany) were determined. Tryptic amidase activity was measured by chromogenic assay using benzoylarginine-*p*-nitroanilide (Trypsin test kit, Boehringer Mannheim). This reports free trypsin and also trypsin-$\alpha_2$macroglobulin complexes, in which the trypsin molecule retains activity against low molecular weight substrates. Dark, haemorrhagic exudates, most often found in fatal acute pancreatitis, interfered with the assay and tryptic amidase could not be determined in such cases.

Free protease activity, the presence of which would indicate overwhelming of the peritoneal antiproteases, was assessed by a fibrin plate technique[20]. The plates were prepared utilizing plasminogen-free fibrinogen (Poviet BV, Holland, supplied by Organon Tecknica, Cambridge, UK). The area of fibrinolysis surrounding the sample application following overnight incubation was compared with varying concentrations of bovine trypsin (ethanol precipitate, Sigma Chemical Co., St. Louis, Missouri, USA). Trypsin–α_2-macroglobulin complexes are formed on the addition of trypsin to fresh plasma and in earlier pilot studies concentrations below 100 μg of bovine trypsin/100 μl plasma did not produce fibrinolysis whereas higher concentrations of trypsin, exceeding the trypsin inhibitory capacity of plasma[21], resulted in fibrinolysis.

Concentrations of α_2-macroglobulin and α_1-antiprotease were measured by conventional rate turbidimetric immunoassay using appropriate anti-human antibodies and standards (Atlantic Antibodies, Winnersh, Berkshire, UK). Eleven patients with acute pancreatitis also had α_2-macroglobulin and α_1-antiprotease assayed in serum sampled at the time of their peritoneal cannulation.

The trypsin inhibitory capacity (TIC) of each of the samples was

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determined using a modification of the fibrin plate technique whereby increasing concentrations of bovine trypsin (0–160 μg) were added to 100 μl of exudate, the concentration at which fibrinolysis first occurred indicating overwhelming of the antiproteases. This provided an overall assessment of the free antiprotease reserve available for binding

Statistical analysis

Results are expressed as medians and interquartile ranges. Differences between groups have been compared using the Mann–Whitney *U* test and by regression analysis.

Results

Pancreatic enzymes

The results of the protein and enzyme assays are shown in *Tables 2* and *3*. Tryptic amidase activity was demonstrated in all pancreatitis exudates in which it could be measured, equivalent to free bovine trypsin concentrations of up to 18 μg/ml (*Figure 1*). None of the pancreatitis exudates demonstrated fibrinolysis.

Four perforated ulcer exudates possessed tryptic amidase activity, one other showing a trace of activity. Two intestinal obstruction exudates possessed a trace of tryptic amidase activity but in neither condition was fibrinolysis demonstrated. Tryptic amidase activity could not be assayed on the exudate from the patient with mesenteric infarction due to its dark, haemorrhagic coloration although this was the only case demonstrating fibrinolysis, equivalent to 270 μg/ml of free bovine trypsin.

Seven of the 11 pseudocyst fluids in which it could be measured possessed tryptic amidase activity. Five demonstrated

Table 1 *Comparison of age, sex, aetiology and complications in relation to the outcome from acute pancreatitis*

	Acute pancreatitis	
	Fatal attacks (*n*=10)	Survivors (*n*=11)
Sex	8 M:2 F	9 M:2 F
Age	59 (55–63)	55 (39–64)
Aetiology		
Gallstones	4	5
Alcohol	2	5
Other	–	1
Unknown	3	–
Gallstones/alcohol	1	–
Median prognostic factor score		
Glasgow (8 factors)*	4 (3–5·5)	2 (2–3)
Ranson (11 factors)†	7·5 (5–9)	3 (1·5–5·5)
Complications		
Fulminant pancreatitis	3	–
Necrosis	5	1
Abscess	1	1
Pseudocyst	–	2
Respiratory insufficiency	1	3
None	–	4

* Glasgow prognostic factor score[18]
† Ranson prognostic factor score[19]

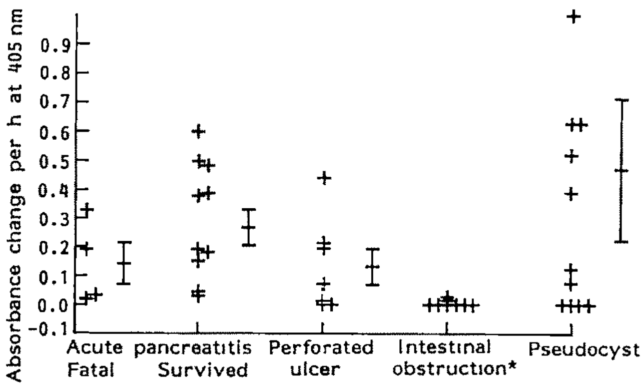

Figure 1 *Tryptic amidase activities in the three peritoneal exudate samples and in pseudocyst fluid. Median activity in intestinal obstruction exudate compared with pancreatitis exudate,* * P<0 001

Table 3 *Comparison of pancreatic enzymes, protein, antiproteases and trypsin inhibitory capacity of exudates from patients with pancreatitis associated with alcohol and gallstones*

	Acute pancreatitis		
Parameter	Alcohol (*n*=7)	Gallstones (*n*=9)	*P*
Total protein, g/l	45 (41–51)	41 (34–43)	0·23
Amylase, units/l	30 000 (22 000–58 700)	14 700 (13 000–35 600)	0·29
Lipase, units/l	37 220 (31 000–38 900)	15 370 (8930–30 400)	0·567
Tryptic amidase, A/h*	0·35 (0·19–0·387)	0·046 (0·029–0·496)	0·37
α_2-Macroglobulin, g/l	0·7 (0·6–0·9)	0·6 (0·4–0·6)	0·055
α_1-Antiprotease, g/l	1·4 (1·4–1·9)	1·8 (1·4–2·2)	0·37
Trypsin inhibitory capacity, μg trypsin/100 μl	60 (30–100)	70 (60–100)	0·43

Values are presented as median (interquartile range). * Units of absorbance change A_{405nm}/h

Table 2 *Comparison of pancreatic enzymes, total protein, antiproteases, and trypsin inhibitory capacity in exudates from patients with acute pancreatitis, perforated ulcer and intestinal obstruction and in pseudocyst fluid*

	Pancreatitis				
Parameter	Dead (*n*=10)	Survived (*n*=11)	Perforated peptic ulcer (*n*=7)	Intestinal obstruction (*n*=8)	Pseudocysts (*n*=12)
Total protein g/l	37·5 (35–41)	45 (41–51)	47 (25–49)	43·5 (41·5–45)	13‡ (5–26·5)
Albumin g/l	23 (21–25)	31 (28–32)	27 (15–30)	25·5 (23·5–26)	6·5† (2–11·5)
Amylase units/l	29 850 (13 330–46 600)	26 000 (14 400–38 000)	1935† (741–13 400)	48‡ (31–142)	67 200 (16 800–189 200)
Tryptic amidase A/h*	0·111 (0·0245–0·258)	0·19 (0·046–0·482)	0·072 (0–0·211)	0‡ (0–0·007)	0·124 (0–0·628)
α_2-Macroglobulin, g/l	0·55 (0·4–0·6)	0·7 (0·6–0·8)	0·9§ (0·6–1·2)	0·6 (0·45–0·8)	0·1† (0·1–0·5)
α_1-Antiprotease, g/l	1·4 (1·4–1·8)	1·7 (1·4–2·1)	1·3 (1–1·6)	1·85 (1·7–2·1)	0·85 (0·5–2·2)
Trypsin inhibitory capacity, μg trypsin/100 μl	60 (30–80)	70 (40–100)	40§ (10–50)	110‡ (100–120)	5‡ (5–10)

Values are presented as median (interquartile range). * Units of absorbance change A_{405nm}/h, § $P<0·05$; † $P<0·01$, ‡ $P<0·001$ compared with pancreatitis exudates. Normal serum ranges: α_2-macroglobulin, 1·1–3·9 g/l; α_1-antiprotease, 1·3–3·2 g/l fibrinolysis, equivalent to free bovine trypsin activities ranging from 13·5 μg/ml to 67 μg/ml, and one other a trace of activity.

Antiproteases

The α_2-macroglobulin concentrations in exudate were typically below the normal range in serum and were significantly lower in fatal pancreatitis compared with the survivors (*Table 2*). In contrast the α_1-antiprotease concentrations were typically within the normal serum range. Concentrations of α_2-macroglobulin in sera from 11 patients with pancreatitis were within the normal range in all but two and were always higher than the corresponding exudates (1·7 g/l (1·2–2·1 g/l) *versus* 0·6 g/l (0·4–0·8 g/l)), $P<0·001$, as were α_1-antiprotease concentrations (2·5 g/l (2·2–3·5 g/l) *versus* 1 7 g/l (1·4–2 g/l)), $P<0·01$.

Trypsin inhibitory capacity

No significant differences were found in the TICs of those with fatal pancreatitis compared with the survivors. However, in three patients who died early, including two dying within 24 h of sampling, the exudates possessed very low TICs (*Figure 2*). Only minor differences were apparent between attacks associated with alcohol or gallstones (*Table 3*) The TICs were found to correlate significantly with the α_1-antiprotease concentrations ($r=0·76$, $P<0·001$) but not with α_2-macroglobulin concentrations.

Perforated ulcer and intestinal obstruction exudates showed respectively significantly lower and higher median TICs (*Table 2*). Eleven of the 12 pseudocyst fluids showed an absent or markedly decreased TIC indicating complete or almost complete consumption of their antiprotease defences (*Figure 2*).

Discussion

The overall TIC rather than the degree of consumption of the individual antiproteases has been examined in the current study. In human serum 90 per cent of the overall TIC is attributed to α_1-antiprotease, α_2-macroglobulin accounting for much of the remainder[22]. The significant positive correlation between α_1-antiprotease and TIC found in the current study suggests that α_1-antiprotease also accounts for much of the TIC in exudate. Lower TICs were found in exudates from patients with pancreatitis and perforated ulcer compared with those with intestinal obstruction indicating a degree of consumption of their antiproteases. As α_2-macroglobulin binds trypsin more readily and becomes complexed first, marked reduction of the TIC, as occurred in three patients with pancreatitis, suggests that actual or incipient overwhelming of α_2-macroglobulin is likely. As was observed in canine pancreatitis[12,13] all three were shocked at the time of sampling, two dying of fulminant pancreatitis within 24 h, the third dying of pancreatic necrosis at the end of the first week. However, low TICs were also recorded in three patients with a perforated ulcer although none manifested shock, as judged by their heart rate and blood pressure, casting doubt on the importance of this phenomenon as an explanation for the systemic toxicity in acute pancreatitis.

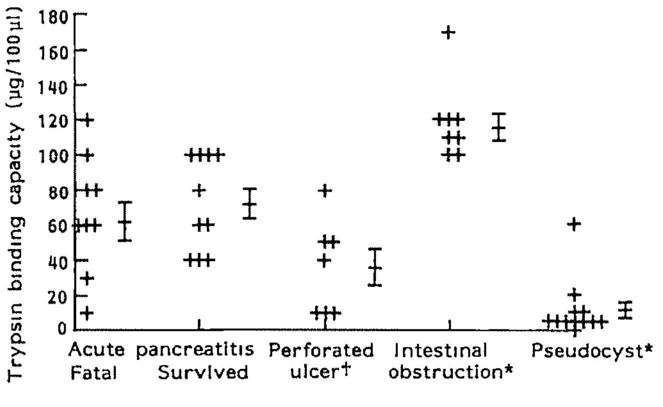

Figure 2 *Trypsin inhibitory capacities in the three peritoneal exudate samples and in pseudocyst fluid Median inhibitory capacities in perforated ulcer exudate, intestinal obstruction exudate and in pseudocyst fluid compared with pancreatitis exudate;* † $P<0·05$, * $P<0·001$

Complete consumption of the antiprotease defences in pancreatitis exudate has not been confirmed to occur, in agreement with Geokas *et al.*[23] but contrasting with the findings of Wendt and co-workers, in which six of 13 exudates sampled at the time of surgery demonstrated free protease activity[20]. It would be unusual to operate early in acute pancreatitis and the exudates may not be comparable with those sampled by peritoneal cannulation soon after admission[23]. No details were provided of their patients' clinical state, when the samples were collected in relation to the onset of the attack, and whether the samples were truly of free peritoneal exudate, loculated peripancreatic collections or even of acute pseudocysts was not clear.

Free protease activity was found in only one exudate in the present study, in a patient with extensive mesenteric venous infarction who was shocked, anuric and *in extremis* when seen. Free protease activity unchecked within the peritoneal cavity was confirmed to be associated with profound systemic toxicity in this one patient but whether responsible for his shocked state, a contributing factor or an unrelated phenomenon is not known.

Free protease activity was a common finding in pseudocysts but when confined within the fibrous cyst wall appeared to pose no threat. There are occasional reports of shock and death in association with acute rupture of a pseudocyst[24] and it may be postulated that this could occur as a result of the sudden escape of a large amount of free protease activity into the peritoneal cavity.

The antiprotease defences appeared to be adequate in the majority of pancreatitis exudates for the degree of proteolytic enzyme release occurring, appearing to be close to being overcome at the time of sampling in only three patients Experimental canine pancreatitis, induced by retrograde infusion of bile, is associated with extensive destruction of the gland and a massive early release of pancreatic enzymes systematically and intraperitoneally, quickly overwhelming the peritoneal antiprotease defences[14]. Such a severe rapidly evolving lesion is presumably a rare occurrence in man, a slower release of enzymes providing time for a protective response by the accumulation of antiproteases within the peritoneal cavity. Continued release of enzymes, or activation of zymogens, perhaps by the action of trypsin–α_2-macroglobulin complexes[25], might lead to overwhelming of the antiprotease defences later during the course of the attack as observed in the closed duodenal loop model of pancreatitis in the dog[12,13]. Equally, the presence of irritant fluid in the peritoneal cavity may lead to continued outpouring of fluid and antiproteases from the peritoneal capillaries which, in most patients, keeps pace with the rate of proteolytic enzyme activation. Replenishment of the peritoneal antiproteases by fresh frozen plasma has been shown to prolong survival from experimental pancreatitis in rats[26] and intraperitoneal antiprotease therapy has been suggested as a treatment in man The results of this study suggest that few patients with acute pancreatitis would be likely to benefit from such an approach.

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Short note

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Abdominal wall dehiscence following Ramstedt's operation: a review of 170 cases of infantile hypertrophic pyloric stenosis

M. H. Harvey, G. Humphrey, N. Fieldman, J. D. George and D. N. L. Ralphs

Department of Surgery, Norfolk and Norwich Hospital, Brunswick Road, Norwich, UK

Correspondence to· Mr M. H Harvey, Westminster Hospital, Dean Ryle Street, London SW1P 2AP, UK

Infantile hypertrophic pyloric stenosis is a common surgical emergency. Ramstedt's pyloromyotomy, the treatment of choice, carries a mortality of less than 1 per cent but morbidity remains significant and the operation has a reputation for the complication of burst abdomen[1] The reason for this has not been explored.

Patients and methods

All cases of infantile hypertrophic pyloric stenosis admitted to the Norfolk and Norwich Hospital from 1978 to 1987 were reviewed retrospectively. Age at presentation, sex, birth rank, weight on admission, feeding and family history were obtained and information on operative technique, suture materials and complications was recorded. Results were analysed using the χ^2 test

Results

During the period under review there were 50 314 live births with a small year to year variation (range 4728–5344). There were 170 cases of pyloric stenosis (2·96/1000 live births) affecting 133 males and 37 females. The average age at presentation was 39·4 days (range 9–121 days) and the average weight was 3 4 kg (range 1·9–7 6 kg). Birth ranks were· 1 (43 per cent), 2 (37 per cent), 3 (13 per cent), 4 (6 per cent) Two cases were 7th born children. First-born males accounted for 34 per cent of cases. At the time of admission 75 per cent of babies were bottle fed. There was a positive family history of pyloric stenosis in 15 per cent.

Diagnosis was made on clinical grounds by palpation of a 'pyloric tumour' in 167 cases. A barium meal was necessary in the remaining three babies to confirm the diagnosis Three babies were successfully treated medically with atropine and the rest underwent laparotomy In three instances details of operative technique were insufficient leaving 164 cases for

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Table 1 *Suture material and closure technique in 164 infants*

Suture material	Mass closure	Layered closure
Chromic catgut	3 (0)	72 (7)*
Polyglactin	12 (1)	23 (0)
Polyglycolic acid	9 (3)	24 (0)
Polydioxanone	3 (0)	0 (0)
Catgut and nylon	–	18 (0)
Total	27 (4)	137 (7)

Values in parentheses are dehiscences; * $P<0.05$ *versus* other suture materials using a layered closure technique (χ^2 test)

analysis. Through an upper transverse incision a standard pyloromyotomy was performed in all cases. The duodenal mucosa was breached and repaired in 21 (12·8 per cent) and five of these babies subsequently developed a wound infection. None developed a total abdominal dehiscence. The overall wound infection rate was 15·5 per cent.

The method of abdominal wall closure is shown in *Table 1*. Total wound dehiscence requiring re-operation occurred in 11 (6·7 per cent) cases. In seven the wound was closed in layers and in four a mass closure was used. Chromic catgut alone was used to close all wounds which dehisced following layered closure. Polyglycolic acid (Dexon® (Davis and Geck, Gosport, UK)) was used in three cases and polyglactin (Vicryl® (Ethicon Ltd., Edinburgh, UK)) in one case in which dehiscence followed a mass closure. No dehiscence was associated with wound infection. The difference between the number of wound dehiscences in the mass closure group and the layered suture group was not significant. There was a significant difference in the number of dehiscences following the use of chromic catgut for layered closure compared with other suture materials ($P<0.05$).

Discussion

The wound infection rate (15·5 per cent) in the present study was higher than in other series which report rates from 1 per cent to 10 per cent[2,3]. The reason for this is unclear as the rate of duodenal perforation was comparable. The rate of abdominal wall dehiscence (6·7 per cent) was similar to those of other series which vary from 0 per cent to 7 per cent[2–5]. The relationship of dehiscence to the technique of abdominal closure and to the suture material used is interesting. It was a surprise to find that wound dehiscence occurred in 14·8 per cent of cases in which a mass closure was used, compared with 5·1 per cent after layered closure.

Mass closure has been found to be satisfactory in adults but its use in infants has not been investigated. The technique was used in only 27 of the present cases but it was used increasingly towards the end of the period of study, reflecting our practice in adults for whom mass closure has become the technique of choice. Technical error might account for the high rate of dehiscence following mass closure although all operations were carried out or supervised by experienced surgeons. Another possible reason was the use of absorbable sutures, although these materials have been shown to afford safe mass closure in adults.

In all seven cases of wound dehiscence following layered closure chromic catgut alone had been used. This suture when used alone has been shown to carry a high risk of abdominal dehiscence in adults and its use has largely been abandoned.

These results suggest that both closure technique and suture material may be important factors in the development of dehiscence. Given the small number of cases in which mass closure was used it would be premature to suggest that this is not a safe method of abdominal closure in infants. However the technique deserves further study and it may be that non-absorbable rather than absorbable sutures should be used. The present data strongly suggest that chromic catgut should not be used for abdominal closure and, if a layered closure is preferred, longer lasting absorbable sutures may offer a safer alternative.

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Neonatal small bowel atresia, stenosis and segmental dilatation

**S. Paterson-Brown,
H. Stalewski and
R. J. Brereton**

*The Hospitals for Sick Children,
London, UK*
Correspondence to:
Mr R. J. Brereton, Department of
Paediatric Surgery, Institute of
Child Health, 30 Guilford Street,
London WC1N 1EH, UK

In 8 years, 44 neonates were treated for small bowel atresia, stenosis or segmental dilatation by one surgical team. There was a single lesion in 30 infants and 14 had two or more sites of intestinal obstruction. Associated gastrointestinal abnormalities were found in 23 (52 per cent) patients. Resection of the atresia(s) and primary anastomosis were performed in 34 infants and staged procedures were carried out in ten patients with complicated lesions. Patients undergoing staged procedures had a higher complication rate than those having primary repair (six out of ten and 11 out of 34 respectively). The overall initial survival rate was 93 per cent, rising to 100 per cent in those without associated anomalies or prenatal complications, but more than a quarter (27 per cent) of survivors have long-term disabilities.

The first successful repair of a small bowel atresia is attributed to Fochens in 1911 but mortality rates in excess of 95 per cent were common as late as 1922[1]. During the past 20 years the mortality rate from this condition has fallen to below 40 per cent[2], attributable to improvements in surgical technique and neonatal intensive care, including parenteral nutrition. Nutritional difficulties may still arise from the short length of gut remaining after surgery or from the loss of particular absorptive properties of areas of missing bowel.

This paper presents the results of a consecutive series of patients with small bowel atresia referred to one surgeon over the past 8 years to examine the associated abnormalities, complications and prognosis. More infants survived than in other series but the survivors had a higher incidence of long-term morbidity than previously reported[1].

Patients and methods

The clinical details of all neonates referred to one surgical team at The Hospitals for Sick Children (Great Ormond Street and the Queen Elizabeth Hospital, Hackney, London, UK) have been prospectively recorded since 1980. Between February 1981 and 1989, 44 neonates were referred with atresia, severe stenosis or segmental dilatation of the small intestine (jejunum or ileum). Patients with isolated duodenal atresia, small bowel volvulus, patent omphalomesenteric duct or Meckel's diverticulum were excluded.

Clinical records were examined retrospectively to study outcome. Patients were regularly reviewed in the outpatient clinic until such time as the clinician thought fit to discharge them from further care. Eight patients no longer attend for review, but in each case the parents and local paediatrician or general practitioner were contacted for progress reports.

The mean age at diagnosis was 1·7 days for atresia and 13 days for stenoses and segmental dilatations (range 1–26 days, the first 24 h after birth being considered as day one). The mean gestational age was 37 weeks (range 32–42 weeks) and mean birth-weight was 2550 g (range 850–4200 g). The main presenting symptoms were bilious vomiting and/or nasogastric aspirate ($n=29$), abdominal distension ($n=22$), ascites ($n=3$), gastroschisis ($n=2$) and symptoms of oesophageal atresia ($n=1$)[1,2]. Two patients had a diagnosis of small bowel atresia suspected at antenatal ultrasound examination, in one a 'double bubble' was observed and fetal ascites was demonstrated in the other.

A single atresia of the jejunum or ileum was present in 29 patients of whom three had additional atresias elsewhere: one of the fourth part of the duodenum, another of the sigmoid colon, and the third of the oesophagus. One infant had a single stenosis of the distal ileum. Two or more atresias of the jejunum or ileum were found in 12 patients and two had several areas of segmental dilatation[3]. The lesions were in the proximal jejunum in 14 patients, in the middle of the small bowel in 13 and in the distal ileum in 17, two of the latter having associated gastroschisis.

Additional abnormalities of the gastrointestinal tract were present in 23 (52 per cent) patients (*Table 1*), the most common being midgut malrotation in 39 per cent[1,2]. At presentation, 12 (27 per cent) had evidence of intestinal perforation (eight free perforation and peritonitis, four meconium cysts) but only one of these infants died. Cystic fibrosis was subsequently diagnosed in four of the five patients with meconium ileus. Other abnormalities not involving the gastrointestinal tract were present in seven patients (*Table 2*).

Primary resection and anastomosis were performed in 34 patients and ten had staged treatment consisting of resection of the atretic segment(s) with exteriorization of the two ends to be followed by delayed anastomosis. All anastomoses were performed using a single layer extramucosal technique[4] and were fashioned end-to-end or end-to-back depending on the discrepancy in diameters of the two ends of the bowel[5].

Results

All 44 neonates, 18 boys and 26 girls, underwent surgery. The initial outcome was unrelated to birth-weight, gestational age or age at diagnosis but was dependent upon the severity of associated anomalies. Three patients, all girls in group C of Nixon and Tawes[2], died in hospital. A girl weighing 1·6 kg with ileal atresia and prenatal perforation associated with prenatal infection died from overwhelming sepsis on the third day after operation; an infant weighing 1·7 kg with ileal atresia and

Table 1 *Associated gastrointestinal abnormalities in 23 patients*

Abnormality	No. of patients*
Malrotation	17
Volvulus	8
Free intestinal perforation	8
Meconium cyst	4
Meconium ileus (four with cystic fibrosis)	5
Apple peel mesentery	5
Gastroschisis	2
Tracheo-oesophageal fistula	1
Duodenal atresia	1
Colonic atresia	1
Anal stenosis	1
Extrahepatic biliary atresia, asplenia syndrome	1
Severe gastro-oesophageal reflux requiring surgery	1

* Some patients had more than one associated anomaly

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Table 2 *Associated anomalies other than cystic fibrosis and those of the alimentary tract in seven patients*

Anomaly	No of patients
Situs inversus, congenital heart disease, polysplenia syndrome	1
Turner's syndrome, mild coarctation aorta	1
Respiratory distress syndrome	1
Bilateral inguinal herniae	1
Syndactyly (colonic atresia)	1
Patent ductus arteriosus, abnormal vertebrae and ribs (oesophageal atresia)	1
Microcephaly and cerebral palsy	1

Table 3 *Early complications*

	After primary anastomosis (11 of 34 patients)*	After staged repair (6 of 10 patients)*
Anastomotic obstruction (requiring reoperation)	4	2
Necrotizing enterocolitis	3	1
Small bowel obstruction (requiring operation)	2	–
Small bowel fistula (requiring operation)	–	2
Asymptomatic radiological leak (no treatment required)	1	–
Adhesive obstruction	–	2
Second operation for colonic atresia	1	–
Wound infection	1	–
Short bowel syndrome	–	1
Infection of central venous feeding catheter	1	1
Peripheral intravenous infusion line abscess	1	1
Chest infection	–	1
Meningitis and/or hydrocephalus	1	1
Apnoea attacks	1	–
Death	2	1

* Some patients had more than one complication

cerebral atrophy died from mediastinitis resulting from a leaking anastomosis following repair of oesophageal atresia with tracheo-oesophageal fistula; and the third girl, weighing 2·9 kg, with proximal jejunal atresia died from pneumococcal intrahepatic abscess and meningitis following portoenterostomy[6] for biliary atresia associated with the asplenia syndrome[7].

Details of the early complications of treatment are shown in *Table 3*. Infants with a birth-weight below 2 kg had more complications after operation than those of greater weight, but the difference was not of statistical significance and was related mainly to the greater severity of associated anomalies in the former group Early complications developed in 29 per cent of boys and in 50 per cent of girls, but the difference was not significantly different. The distended gut proximal to the anastomosis was tapered[5] in eight patients, one of whom developed an asymptomatic radiological leak. Although the complication rate for staged treatment (six out of ten patients) was higher than that for resection and primary anastomosis (11 out of 34 patients), the difference was not statistically significant. More than 10 cm of gut was resected in 18 patients and 25 (57 per cent) infants received total parenteral nutrition. Only one wound infection occurred

An uneventful recovery, without either early or late complications, occurred in only 17 (39 per cent) patients Of the 41 survivors, delayed complications developed in 12 (*Table 4*) of whom four have long-term gastrointestinal problems: a girl with short bowel syndrome has required repeated hospital admissions over the past 6 years for additional surgery and intermittent parenteral nutrition with its associated complications; a boy has failure to thrive and developmental delay at 18 months; another boy has chronic diarrhoea of unknown aetiology; and a boy with gastroschisis and chronic diarrhoea requires vitamin supplementation. In addition, six infants with severe associated anomalies will fare less well in the future: two boys and two girls have cystic fibrosis; a girl with two midjejunal atresias and prenatal microcephaly has severe mental retardation; and a girl with ileal segmental dilatation and Turner's syndrome is developing with apparently normal intelligence but will require endocrine supplements in early teenage years. The girl with polysplenia syndrome is at long-term risk of pneumococcal infection and was seriously ill with various infections, including meningitis, after corrective surgery for associated congenital heart disease Although late problems and complications were more common in girls than boys (52 *versus* 33 per cent), the difference was not statistically significant.

Discussion

Although two patients with segmental dilatation[3] have been included in the series this is justified because the associated surgical problems are similar to those of patients with either atresia or stenosis[1]. A major advance in the management of these infants was the introduction of regional centres for neonatal surgery following the pioneering work of Forshall and Rickham[8].

For infants born with intestinal atresia or stenosis during the past two decades, there have been progressive improvements in survival rates from 62 per cent in 1971[2], to 75–77 per cent by 1981[9,10], to 87 per cent by 1984[11] and more recently to 89 per cent[10,12]. In the present series an overall initial survival rate of 93 per cent was achieved, and 100 per cent survival in those without prenatal complications or associated anomalies[1,2,10,12]. These improvements may be attributed to recent advances in anaesthetic techniques and intensive (nursing) care including parenteral nutrition[10,11]. Total parenteral nutrition was required by 57 per cent of our patients, in one for up to 2 years continuously and intermittently for a further 4 years. Generally, infants with high jejunal lesions have more associated anomalies, more anastomotic complications and a worse prognosis than those with distal ileal lesions[2,10], but two of the three deaths in our series occurred in girls with ileal lesions. The male:female sex ratio of 2:3 has been reported in some[2], but not all[12], British series but the tendency for girls to have higher mortality and morbidity rates than boys has not been recorded elsewhere. There is a tendency for girls to have proportionally more complicated and multiple lesions

Table 4 *Delayed complications after discharge from hospital in 12 patients*

Complication	No of patients
Short bowel syndrome	1
Incisional hernia	1
Necrotizing enterocolitis (primary repair)	1
Small bowel obstruction (operation not required)	2
Small bowel obstruction (operation required)	2
Recurrent chest infections, failure to thrive, developmental delay	1
Cardiac surgery (congenital heart disease)· polysplenia syndrome	1
Chronic diarrhoea, vitamin supplements required (gastroschisis)	1
Chronic diarrhoea	1
Chest infections, gastro-oesophageal reflux	1

than boys, who often have but a single atresia[12]. To date, no late deaths have occurred[11].

As expected, few survivors with isolated atresia have developed long-term gastrointestinal problems[1,9–11]. The majority (26 patients) lost less than 10 cm of small bowel even when the dilated proximal segment was resected[2,13,14]. Whenever possible an end-to-end anastomosis was constructed using interrupted extramucosal sutures[4,9,15,16]. In the presence of proximal jejunal atresia with marked discrepancy between the diameters of the two ends of bowel a tapered anastomosis may be the treatment of choice[5,9,11,12]. In the absence of associated anomalies, the mortality rate for primary repair should be very low but in the presence of other gastrointestinal anomalies staged repair may be the safer option when facilities for parenteral nutrition are available[9,10,12]. In this group of infants severe fluid and electrolyte losses reported by some authors[1] were not encountered. This may be because of improved methods of parenteral nutritional support and the fact that all stomas were closed within a few weeks, once the complicating factors had resolved.

Anastomotic malfunction requiring reoperation occurred in 12 per cent of the patients with a direct anastomosis, marginally lower than in other series[10,12]. This complication is most common (20 per cent) in those with high jejunal atresia[9,10], especially those with prenatal midgut volvulus necessitating jejunocolic anastomosis. Vented anastomoses[17,18] are not recommended because of the high complication rates[9,10,12]. Infants, usually girls, with 'apple peel' atresia are said to have a poor prognosis[19] but this has not been our experience[9,12] and affected infants in this series did well.

Even when considerable amounts of bowel were resected, or had been resorbed prenatally, very few problems were encountered in infants having more than 75 cm of remaining bowel, provided that both jejunum and ileum were present[1,11,12,20–27]. One girl with prenatal midgut deletion[28] was born with only 35 cm of distended jejunum. She spent the first 2 years of life in hospital undergoing 11 major abdominal operations, including intestinal lengthening[29], and a further five operations, with associated complications[30], for insertion of central venous catheters. Currently she receives nocturnal parenteral nutrition at home. Her growth is restricted but her mental development is normal and she attends an ordinary primary school The only other infant with less than 50 cm of remaining small bowel died from complications arising from the treatment of biliary atresia. Children with extensive intestinal resections, mainly of the ileum, are at risk of developing fat-soluble vitamin deficiencies leading to rickets, osteomalacia, night-blindness and blood clotting problems, and to megaloblastic and iron deficiency anaemias[12,22,24,26,27]. In adolescents gallstones and renal calculi may develop[23,31,32]. There may be an increased risk of colorectal carcinogenesis in later life[33].

Necrotizing enterocolitis[34] developed after operation in five (11 per cent) patients; all were treated non-operatively and all survived, but one subsequently underwent reoperation for anastomotic complications. Necrotizing enterocolitis is a major cause of morbidity and death in neonates with small bowel atresia[9], especially those with gastroschisis[10,12,34,35] or apple peel mesentery[12,34,35]. One of the infants in this series developed enterocolitis after discharge from hospital, a well known complication of neonatal surgery[34].

At least 10 per cent of patients with meconium ileus have an intestinal atresia and perforation[36,37] and 9 per cent of our patients with atresia had cystic fibrosis, a relatively low incidence compared with other series[18,37]. Meconium peritonitis and intestinal malrotation causing midgut volvulus are common associated anomalies in this group of infants[1,36,37]. All four of our patients had jejunal atresia. Two infants had the two ends of bowel exteriorized, followed by delayed anastomosis and uneventful recovery. Another underwent resection of the atresia, saline lavage of the distal bowel and end-to-end anastomosis. The fourth had ischaemia of much of the jejunum and had an extensive jejunal resection with Bishop–Koop anastomosis[17] This infant was treated at the beginning of the series and more recently we have tried to avoid extensive intestinal resections and vented anastomoses[9,10,12,17,18,36–38]. Two of these patients had attacks of postoperative necrotizing enterocolitis. To date, only one has developed long-term gastrointestinal problems and another requires vitamin E supplements for ataxia[39], but all regularly take pancreatic extract.

With early diagnosis and surgery[40], and in the absence of short bowel syndrome, patients with isolated atresias of the small bowel have a good long-term prognosis with low mortality and morbidity rates but the presence of associated abnormalities[1,2] has a major bearing on the long-term result in some patients, especially those with high jejunal lesions[9,10,12,21]. Improvements in survival rates of infants with associated anomalies, short bowel syndrome or specific absorptive deficiencies, possibly resulting in long-term metabolic problems or carcinogenesis, explain the apparent paradox whereby, as the results of neonatal treatment have improved, the requirements for long-term review of surviving children have increased rather than lessened.

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Primary papillary carcinoma of a thyroglossal duct cyst: report of a case and literature review

S. D. Weiss and
C. C. Orlich*

*Department of Surgery, Contra Costa County Hospital, Martinez, California, and *General Surgery Service, Hospital San Juan de Dios, San José, Costa Rica*

Correspondence to:
Stephen D. Weiss, 322 Primrose Place, Pleasant Hill, CA 94523, USA

Thyroglossal duct cysts are the most common anomaly in thyroid development. They are twice as frequent as branchial cleft abnormalities and, in children, are second only to enlarged cervical lymph nodes as the cause of neck mass. Generally, duct cysts are benign, but 1 per cent of cases may be malignant. From the world literature, 114 cases of malignant thyroglossal cysts were available for review. With the addition of our own case, we discuss 115 instances of duct cysts. The different types of neoplasia described included thyroid papillary carcinoma in 81·7 per cent, mixed papillary-follicular carcinoma in 6·9 per cent, squamous cell carcinoma in 5·2 per cent, follicular and adenocarcinoma in 1·7 per cent each, and malignant struma, epidermoid carcinoma and anaplastic carcinoma in 0·9 per cent each. Of the 115 cases surveyed, 35 thyroid glands were examined microscopically; of these, four (11·4 per cent) contained malignant foci. Whether these are primary malignancies of the thyroglossal duct cysts or metastases is discussed.

In 1911, Brentano reported the first case of a neoplasm arising in a thyroglossal duct cyst. Since that date, increasing numbers of cases have been reported as a result of a greater awareness of the malignant potential of thyroglossal duct cysts, and a more thorough search of the pathology specimens.

During the first week of embryological development, the thyroid gland attains its final normal position in the neck by downward migration of a median anlage arising from the foramen caecum in the base of the tongue. The pyramidal lobe of the thyroid is formed by descending through the second branchial arch to just in front of the second to sixth tracheal rings. The second branchial arch gives rise to the tissue that later forms the hyoid bone, which may surround the duct or pass it anteriorly or posteriorly[1,2]. Ordinarily, the duct itself disappears at the sixth or seventh week of fetal life[3], but occasionally it can persist. In this case, thyroid cells seeded during the process of descent may later proliferate and become functional. The persistent thyroglossal tract may then dilate to form a cyst. This is the most common anomaly in thyroid development. Thyroglossal duct remnants are twice as frequent as branchial cleft abnormalities[4] and are second only to enlarged cervical lymph nodes as the cause of masses in the neck in children[5].

Positive identification of a thyroglossal duct cyst is accomplished by demonstrating epithelial lining of the duct or cyst and normal thyroid follicles in the wall of the cyst[6,7]. Wide variations are seen in the epithelial lining of such cysts. In one series, the most common lining was stratified squamous epithelium, followed by pseudostratified, simple cuboidal and transitional epithelium[8]. Moreover, typical mucous and seromucinous salivary glands have been identified in the cyst wall[3,7,9–11]. Although gastrointestinal epithelium is common in branchogenic and dorsal enteric mediastinal cysts, it is extremely rare in thyroglossal duct remnants. Such a cyst with epithelium from the small intestine has been described[12]. Furthermore, a cyst containing gastric epithelium in its lining has been reported with special reference to its potential for acid and pepsin production, which in turn may produce peptic ulceration, tracheal penetration, massive haemorrhage and death[12].

Benign thyroglossal duct cysts are treated surgically. In 1928, Sistrunk described a procedure to excise these cysts. This included resection of the cyst and tract, extending to the foramen caecum at the base of the tongue in continuity with the midportion of the hyoid bone. More than 60 years later, this procedure has not been modified.

Case report

A 41-year-old man was seen at the Hospital San Juan de Dios in San José, Costa Rica, for a neck mass he had noted incidentally 1 month earlier. He was asymptomatic. On physical examination, a mass of 4 × 5 cm was evident in the anterior midline of the neck. The mass was rubbery, was not tender, and was easily displaced by palpation. Vertical motion of the mass was present upon deglutition or protrusion of the tongue. The thyroid gland was normal and there was no palpable cervical lymphadenopathy. The patient was admitted with the diagnosis of a thyroglossal duct cyst and had *en bloc* excision as described by Sistrunk. The thyroid was examined at operation and was normal.

A pathological examination of the thyroglossal cyst found a small, warty excrescence within the lumen. This was identified as a thyroid papillary carcinoma on histological sectioning (*Figure 1*). Normal epithelium and normal ectopic thyroid tissue were also identified within the cyst (*Figure 2*).

The patient was readmitted and had near total thyroidectomy. The regional lymph nodes were palpated and found to be normal, and no biopsy was deemed necessary. Serial sections of the entire gland revealed a normal thyroid with no evidence of neoplastic foci.

Review of reported cases

With the addition of our own case to 114 published cases available for review[2,3,6,8–10,12–15], the total number of patients discussed is 115. Of the 115 patients, the female:male ratio was 3:2. The median age was 38 (range 6–84) years. The excised cysts were 1–12 cm in size. More than 80 per cent of the cysts were 2–5 cm in size.

In most cases, the thyroglossal duct cysts became manifest as an asymptomatic mass. Occasional symptoms included dysphagia, dysphonia, a draining sinus and recent change in

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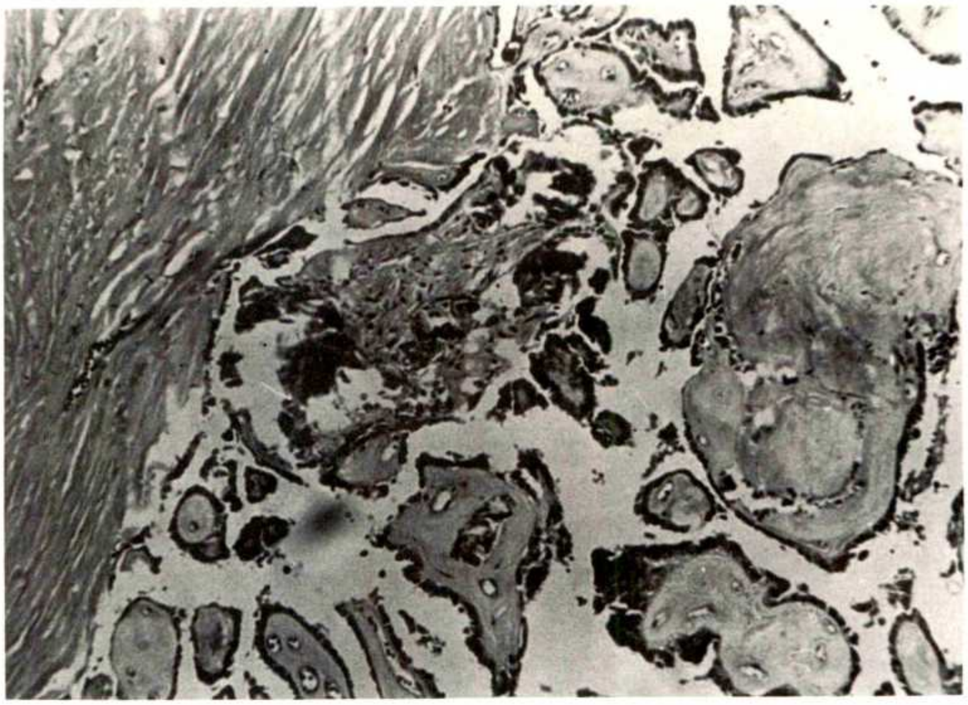

Figure 1 *Photomicrograph showing papillary carcinoma originating in cyst wall*

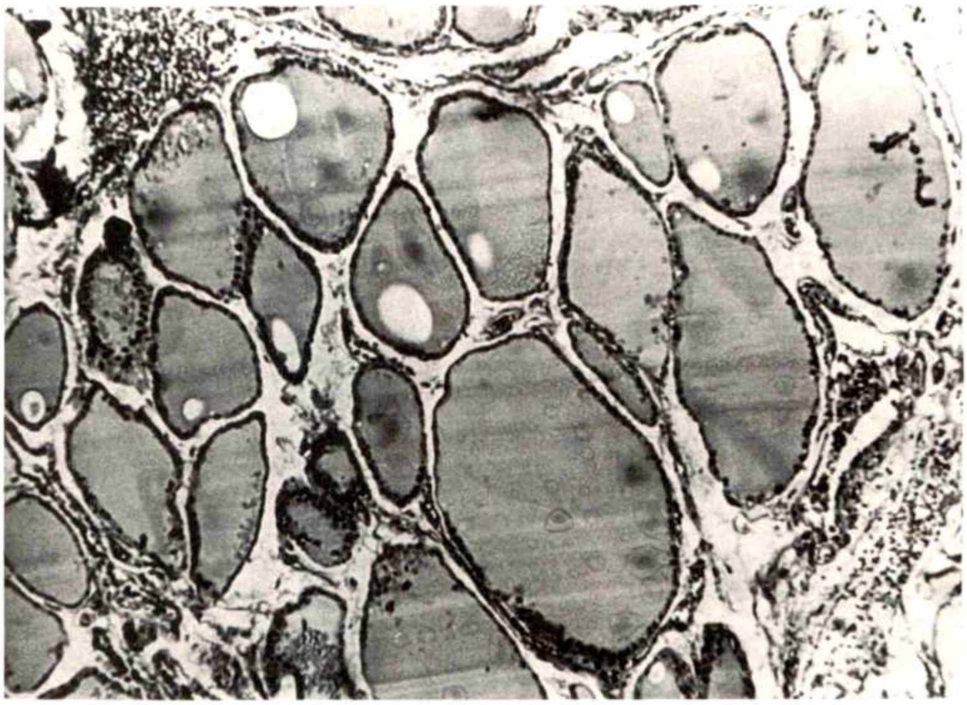

Figure 2 *Photomicrograph showing ectopic thyroid tissue in cyst*

size of the mass. Nearly 90 per cent of the cysts had been present for more than 1 month.

The pathological diagnoses of the malignancies found within the cysts included papillary carcinoma in 94 patients (81·7 per cent), mixed papillary-follicular carcinoma in eight patients (6·9 per cent), squamous cell carcinoma in six patients (5·2 per cent), follicular carcinoma in two patients (1·7 per cent), adenocarcinoma in two patients (1·7 per cent), and single occurrences (0·9 per cent each) of malignant struma, epidermoid carcinoma and anaplastic carcinoma. Twenty-four patients had local invasion through the cyst wall and into surrounding tissues (including strap muscles) or vascular invasion. Thirteen patients had one or more metastatic lymph nodes.

Thirty-five thyroids were serially examined microscopically, 33 from thyroidectomies (including our case) and two from autopsies. Only four (11·4 per cent) of the 35 thyroids contained malignant foci (three had papillary carcinoma and one had mixed papillary-follicular carcinoma). One additional patient who manifested a thyroid nodule 6 years after the initial Sistrunk procedure had thyroidectomy and was found to have a papillary carcinoma[9].

Twenty-eight patients had thyroid scintiscans either before or after removal of their thyroglossal duct cysts. All were normal except two who showed 'cold' nodules. These two had thyroidectomies: one, who had a squamous cell carcinoma diagnosed within the cyst, was found to have a benign multinodular gland; the other, who had an anaplastic carcinoma in the cyst, was shown to have a benign follicular adenoma of the thyroid gland.

The management of each patient varied widely. Seventy-five patients had an initial Sistrunk procedure, 25 had local excision, and the remainder had other procedures. Twenty-nine patients had subsequent procedures such as thyroidectomy, re-excision or cervical lymph node dissection. Almost half of the patients who had some form of lymph node dissection ('berry picking' or sampling, radical or modified radical, unilateral or bilateral) had metastatic disease. Adjuvant medical management included suppression with exogenous thyroid supplementation in 24 patients, radio-iodine treatment in 10 patients and external radiation therapy in six patients

The follow-up period also varied widely and was reported to be as short as 2 months and as long as 28 years. Most patients were well for the period during which they were followed.

Discussion

Primary carcinoma of the thyroglossal duct should conform to the following diagnostic criteria: (1) localization of the carcinoma to a clearly demonstrable thyroglossal duct as defined previously, and (2) no carcinoma at histopathological examination of the thyroid gland[16].

Whether carcinomas in the thyroglossal remnants originated primarily in this tissue or represented metastasis from the thyroid gland is an important issue. A papillary carcinoma separate from the main thyroid gland raises the possibility of an occult primary carcinoma in the thyroid[7,17–20]. Papillary carcinoma of the thyroid may indeed metastasize without a detectable lesion in the gland itself[17] Crile[21] believed that the thyroglossal duct could act as a natural conduit for spread of thyroid carcinomas. Judd[22] and Nuttall[23] believed the metastatic theory.

The rather frequent finding of normal thyroid follicles in association with carcinomas in thyroglossal duct cysts suggests that they arise primarily from the cysts. Of the cases discussed here in which the thyroid gland was microscopically examined, only 11·4 per cent had foci of carcinoma present, which suggests a primary origin for the thyroglossal duct carcinoma in 88·6 per cent. The cases found to have neoplastic foci in the thyroid gland may represent metastasis from a primary carcinoma in the cyst, two independent primary carcinomas (multicentric), or indeed a primary thyroid carcinoma.

In most of the cases reviewed, as well as in our own, the diagnosis of malignancy was not suspected before operation. Carcinoma was identified only at pathological examination. They were indistinguishable clinically. Patients were asymptomatic in most cases. Clinical correlation between size and change in size as an indicator of carcinoma is not a reliable finding[4,9]. Nevertheless, carcinoma should be suspected in any thyroglossal duct cyst which is hard, fixed, irregular or has undergone recent change[24]. The presence of enlarged palpable lymph nodes in the neck should suggest malignancy[6,25]. Metastasis to regional lymph nodes was present in 11·3 per cent of cases reviewed (13 of 115), and about half of these were suspected before operation. A history of irradiation to the neck or mediastinum during childhood or adolescence should arouse suspicion of carcinoma because this is a known risk factor for papillary thyroid cancer[24].

Carcinoma of the thyroid is a slow growing, malignant tumour that may progress for 20 years or more, spreading infrequently to regional lymph nodes before it metastasizes to distant sites such as lung, liver or bone[2,4,13–16,19]. Primary papillary carcinoma of a thyroglossal duct cyst should not be expected to behave differently.

Treatment by the Sistrunk procedure is suggested for non-metastatic disease. Thyroidectomy is recommended only if there is objective suspicion of a mass or nodule in the gland (e.g. 'cold' nodule on scan, palpable mass or history of radiation). Radical or modified radical neck dissection is indicated only in the presence of positive lymph nodes. Because of the prolonged course of papillary carcinoma (20 years or more), long-term follow-up is recommended.

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Solitary thyroid nodule: a prospective evaluation of nuclear scanning and ultrasonography

The aim of this study was to assess prospectively the value of thyroid nuclear scans and ultrasound examination in the preoperative investigation of patients with a solitary thyroid nodule. Total thyroid lobectomy for a solitary thyroid nodule was performed in 68 cases. Each patient had a thyroid isotope scan (except two women who were pregnant) and thyroid ultrasound examination. There were 10 (15 per cent) malignant nodules, 11 (16 per cent) benign neoplastic nodules and 47 (69 per cent) benign non-neoplastic nodules. All of the patients with malignant nodules who were scanned had a solitary cold nodule on thyroid scan, as did 40 (69 per cent) of those with benign solitary nodules. Ultrasound examination of the thyroid suggested correctly that one of 16 (6 per cent) cystic lesions, four of 16 (25 per cent) complex solid-cystic lesions and three of 18 (17 per cent) of solid lesions were malignant. One lesion reported as multinodular on ultrasonography and one reported as normal also turned out to be malignant. Thyroid isotope scans and ultrasound do not accurately differentiate between benign and malignant conditions and their routine use in the investigation of a solitary thyroid nodule should be abandoned.

M. R. Cox, S. G. Marshall and R. A. J. Spence

Belfast City Hospital, Belfast
BT9 7AB, UK
Correspondence to:
Mr R. A. J Spence

Management of the solitary thyroid nodule poses a problem for the clinician in the selection of patients who require surgery. Only 10–20 per cent of solitary thyroid nodules are malignant[1–5] and clinical history and examination are frequently unable to distinguish between benign and malignant thyroid nodules[6,7]. Thyroid nuclear scans and ultrasonography have been the main non-invasive investigations used to select patients for surgery[8–13]. Cold solitary nodules on nuclear scans are the most common finding in malignant thyroid nodules[8,9,13–16]. In the past, a cystic nodule on ultrasound examination would have been assumed to be probably benign[9,10]; however the incidence of malignancy in cystic nodules is higher than generally accepted[17]. There are many conflicting reports discussing the usefulness of thyroid isotope scans and ultrasonography in the investigation of the solitary thyroid nodule[2–4,7,8,10–13]. The aim of this study was to assess prospectively the usefulness of thyroid scans and ultrasonography in the investigation of a solitary thyroid nodule.

Patients and methods

In a prospective analysis all patients presenting with a solitary thyroid nodule between August 1986 and December 1989 were investigated by thyroid nuclear scan (technetium) and thyroid ultrasonography Patients with pressure symptoms or an obvious malignancy on examination were excluded as these patients required surgery on clinical grounds. All patients were clinically and biochemically euthyroid.

During this 41 month period a total of 158 patients underwent thyroid surgery, in 79 of these patients this was undertaken for a solitary thyroid nodule. Eleven of these 79 were excluded from the study on the basis of pressure symptoms or obvious malignancy As fine needle aspiration cytology (FNAC) was not available at the time of study all the remaining 68 patients with a solitary thyroid nodule underwent total thyroid lobectomy. Hence a histological diagnosis was available in all 68 patients.

Thyroid isotope scans were performed and reported by one experienced consultant radiologist Technetium was used for all scans as it is less toxic and less expensive than other isotopes and easily available Scans were reported as showing a solitary cold nodule, unilateral increase in size with normal uptake, a solitary warm or hot nodule, irregular uptake in the gland or a normal appearance.

All thyroid ultrasound scans were performed using a high frequency (7 5 MHz) real time scanner (Diasonics Imager 100, Diasonics Sonotron, Bedford, UK) with a sector probe. Scans were reported as showing a solitary solid nodule, a complex solid-cystic nodule (a nodule which was predominantly solid with some cystic areas within it), a cystic nodule, multiple nodules or normal appearances. All ultrasound scans were performed and reported by one of two experienced consultant radiologists

At the commencement of this study FNAC was not available. An experienced consultant cytopathologist began to attend the head and neck clinic in April 1989, after which all patients had FNAC of their thyroid nodule in addition to a thyroid scan and ultrasonography. The FNAC results were recorded prospectively. The advent of this diagnostic method led to a new bias in patient selection for surgery and the study was concluded in December 1989.

Results

The female to male ratio was nine to one and the mean patient age was 48·6 years. The histological diagnoses are shown in *Table 1*. There were ten (15 per cent) malignant nodules: seven papillary, two follicular and one secondary carcinoma[17] In addition to the malignant nodules there were 11 (16 per cent) benign neoplasms, giving a total of 21 (31 per cent) neoplastic lesions. This left 47 (69 per cent) patients with benign, non-neoplastic lesions.

Of the 68 patients 66 had thyroid isotope scans; the two patients who did not have thyroid scans were pregnant at the time of presentation and both had a papillary carcinoma. The scan results are summarized in *Table 2*. The remaining eight patients with malignant nodules who had a nuclear scan all had a solitary cold nodule on thyroid scan. Forty patients with benign lesions also had a solitary cold nodule on thyroid scanning. Combining the patients with benign and malignant

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Table 1 *Histological diagnosis of solitary thyroid nodules*

Histological diagnosis	Number	Mean age (years)
Malignant		
Papillary carcinoma	7 (10)	42·2
Follicular carcinoma	2 (3)	54
Secondary carcinoma	1 (2)	54
Benign neoplastic		
Follicular adenoma	10 (15)	52·8
Hurthle cell adenoma	1 (2)	
Benign non-neoplastic		
Multinodular goitre	17 (25)	51
Colloid nodule	16 (24)	47·1
Degenerative nodule	7 (10)	46·3
Hashimoto's thyroiditis	6 (9)	51·8
True thyroid cyst	1 (2)	18
Total	68 (100)	48 6

Values in parentheses are percentages

Table 2 *Results of thyroid nuclear scans in 66 patients with solitary thyroid nodules*

Scan report	Malignant	Benign	Neoplastic	Non-neoplastic
Cold nodule	8	40	16	32
Unilateral increase in size	0	9	3	6
Unilateral irregular uptake	0	6	0	6
Normal	0	3	0	3
Total	8	58	19	47

Two patients with papillary carcinoma did not have a nuclear scan as they were pregnant at the time of presentation

Table 3 *Results of both thyroid scanning and ultrasonography in the solitary thyroid nodule*

Result	Malignant	Benign	Neoplastic	Non-neoplastic
Cold non-cystic	7	26	15	18
Cold cystic	1	12	1	12
'Not cold' non-cystic	0	17	2	15
'Not cold' cystic	0	3	1	2
Total	8	58	19	47

Two patients did not have thyroid scans as they were pregnant at presentation

neoplasms, 16 had a solitary cold nodule, with the remaining three patients having a scan with a unilateral increase in size and normal tracer uptake. Thirty-two patients with a benign, non-neoplastic lesion had a solitary cold nodule on thyroid scanning. The remaining nine patients with benign lesions had either unilateral irregular uptake or a normal scan.

All 68 patients had thyroid ultrasonography performed. The results according to malignant *versus* benign diagnoses and neoplastic *versus* non-neoplastic diagnoses are summarized in *Table 3*. Eighteen of the solitary thyroid nodules appeared to be solid, 16 were solid-cystic, 16 were cystic, 13 were multinodular and five were normal. Three of 18 (17 per cent) patients with a solid lesion, four of 16 (25 per cent) with a solid-cystic lesion, one of 16 (6 per cent) with a cystic lesion, one of 13 (8 per cent) with a multiple nodules and one of five (20 per cent) with a normal thyroid on ultrasonography were subsequently found to have a malignant thyroid nodule. There was no ultrasonographic appearance which was associated exclusively with a benign or malignant lesion.

Discussion

The aim of investigation in patients with a solitary thyroid nodule is to operate on as few patients as possible without missing any cases of malignancy. Thyroid nuclear scans had 100 per cent sensitivity in this series, in that all malignant nodules were detected as solitary cold nodules. There were no warm or hot nodules in this series. The incidence of carcinoma in a 'hot' nodule is reported to be about 4 per cent[13,18] As only 4–7 per cent of all solitary thyroid nodules are 'hot'[13,14], the overall incidence of a 'hot' malignant nodule is less than 0·2 per cent. The specificity of thyroid scans in this series was low with only 17 per cent of solitary cold nodules being malignant. This result is similar to that of other reports which cite an 11–17 per cent incidence of malignancy in solitary cold thyroid nodules[7,11,16]. The specificity of thyroid scans is improved if the scan is used to discriminate between neoplastic and non-neoplastic lesions, with one-third of cold solitary nodules being neoplastic, leaving two-thirds of solitary cold lesions which are non-neoplastic. To our knowledge no previous report has looked at the accuracy of thyroid scans in discriminating between neoplastic and non-neoplastic thyroid nodules. Most benign neoplastic solitary thyroid nodules are follicular adenomas[19–21] which can be difficult to distinguish from carcinomas on histological section and cannot be distinguished with FNAC[7,19,22–24]. Thyroid nuclear scans revealed that 16 of 19 (84 per cent) neoplasms in this series were solitary cold nodules whereas all eight malignant nodules scanned showed up as solitary cold nodules Three benign neoplastic nodules were not detected by thyroid isotope scans.

Although in this series no malignant lesion was 'cool' or normal on isotope scan, three of the ten benign adenomas were reported to have normal tracer uptake. Some larger series report that 7–9 per cent of solitary nodules found to be 'cool' or normal on nuclear scan are malignant[4,13]. One (6 per cent) lesion which was cystic on ultrasonography in this series turned out to be malignant. This has been the experience of many authors in that 7–21 per cent of lesions reported as cystic on ultrasonography turn out to be malignant[8,12,25].

Complex solid-cystic lesions are predominantly solid with areas of cystic change within the nodule[7,12,16]. Of such nodules 12–20 per cent are malignant[7,12,26], an incidence which is slightly lower than in our series The incidence of malignancy in solid lesions is between 10 and 21 per cent[7,12,16,26], a finding consistent with our data. The incidence of malignancy in nodules reported as multinodular on ultrasound examination has to our knowledge not been reported previously. Not all nodules with a multinodular pattern can be assumed to be benign. The malignant nodule reported as multinodular in appearance turned out to be a metastatic deposit from a hypernephroma and this patient has been reported recently[18]. The incidence of metastatic carcinoma in the thyroid is low[12,13] but such deposits are normally described as either solid or solid-cystic in appearance[12].

Ultrasonography of the thyroid is accurate in determining the physical characteristics of isolated swellings, but inaccurate in predicting the presence of neoplasia[27]. Most of the solid and solid-cystic lesions are not malignant[7,12,16,26], and some cystic lesions are not benign[8,17,25].

The use of needle aspiration in cystic lesions, first described by Crile[28], and the subsequent acceptance of fine needle cytology to evaluate solitary thyroid nodules, has meant that ultrasonography is now of little use in the investigation of solitary nodules. Aspiration of a thyroid cyst is better than ultrasound examination in that it gives a sample for cytological examination[13,24,29] and also may treat the nodule[13,29]. However, cytological examination in cystic thyroid nodules is less accurate than in solid nodules[29]. Cystic lesions with benign cytology which do not completely resolve with aspiration, which quickly recur after one aspiration or which recur after two aspirations should be excised. Malignant nodules will not be overlooked when using this approach[12,13,20].

Some authors argue that newer, more accurate ultrasonography equipment allows the detection of smaller (down to 1 mm) nodules, some of which are small papillary carcinomas[10,30,31]. Post-mortem studies reveal that 4·2 per cent of all patients having an autopsy where no thyroid nodule was detected clinically have small thyroid carcinomas[32]. The clinical relevance of these small nodules seen on modern ultrasound is questionable but is unlikely to be of clinical importance.

Early reports suggest that follicular adenomas of the thyroid had a characteristic appearance which was called the 'halo sign'[33]. If this were accurate it could be used to distinguish between benign and malignant follicular neoplasms found on FNAC. However, more recent reports have shown that the halo sign is not an accurate indicator of a benign follicular neoplasm, with 10–20 per cent of lesions being malignant[12,25,33–35].

The false negative result of FNAC is low 0–2·1 per cent) in most large studies[13,16,19,21,24,36]. Sampling error is one explanation for such false negative results[13,29,37] but no study has yet been performed to show that ultrasound guided FNAC will significantly lower this false negative rate. Overall, we conclude, with others[7,8,12,16,19,25,26,33,35], that ultrasonography has little or no place in the investigation of the solitary thyroid nodule as it cannot differentiate between benign and malignant, or between neoplastic and non-neoplastic solitary nodules, provided FNAC is available.

The combination of isotope and ultrasound scanning does not offer any additional benefit in the investigation of the solitary thyroid nodule. From our results, only 20 (29 per cent) of lesions could be accurately identified as benign before surgery. All these lesions had a thyroid scan which showed that the nodule was not a solitary cold nodule.

Only 85–90 per cent of malignant thyroid nodules are cold nodules[4], hence using isotope scanning to select thyroid nodules for FNAC will miss 10–15 per cent of the malignant nodules. About 30 per cent of follicular adenomas are functional and are either normal or hot on isotope scans[9,13]. One report used FNAC initially and then submitted all nodules found to be follicular neoplasms to isotope scanning, operating only on those where the nodule had been shown to be cold[23]. This risks missing about 10 per cent of follicular carcinomas which are not hypofunctioning on thyroid scanning[4].

Thyroid isotope scans and ultrasonography have little place in the routine management of the solitary thyroid nodule, as they do not accurately select which patients require surgery. Even where a cytopathologist is not available, thyroid ultrasonography is of little use as attempted aspiration of solitary nodules will define and treat most cystic nodules. Thyroid nuclear scanning may select out a small number of cases not requiring surgery but at the risk of overlooking 7–9 per cent of malignant nodules[4,13]. Therefore in the presence of FNAC with an experienced cytologist the routine use of thyroid scanning can probably be abandoned.

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DNA aneuploidy in follicular thyroid neoplasia

E. L. Cusick,
S. W. B. Ewen*,
Z. H. Krukowski and
N. A. Matheson

Departments of Surgery and
**Pathology, University of*
Aberdeen, Aberdeen, UK
Correspondence to:
Mr N. A. Matheson, Consultant
Surgeon, Ward 49, Aberdeen
Royal Infirmary, Foresterhill,
Aberdeen AB9 2ZB, UK

The potential value of DNA aneuploidy, in distinguishing benign from malignant follicular thyroid neoplasms, was studied. The nuclear DNA content of 65 follicular thyroid neoplasms (52 adenomas and 13 carcinomas) was determined by flow cytometric analysis of paraffin embedded material; in 58 cases preparations were technically satisfactory. In 22 follicular neoplasms DNA analysis was also performed on fresh material obtained by fine needle aspiration of surgical specimens. Cell cycle analysis was performed on both fresh and fixed specimens. An aneuploid DNA profile was found on analysis of fixed tissue in eight of 45 (18 per cent) follicular adenomas and four of 13 (31 per cent) follicular carcinomas. DNA aneuploidy was also found in six of the 22 (27 per cent) fresh preparations from follicular adenomas. The frequency of DNA aneuploidy in apparently benign and malignant follicular neoplasms was similar. Follicular thyroid neoplasia are best regarded as a single entity with a low incidence of local and distant spread. All follicular neoplasia are therefore best excised.

Follicular thyroid neoplasms are common: approximately 25 are removed annually in the north-east of Scotland. The majority of these are apparently benign adenomas with only a small number of follicular carcinomas (mean 4·5 per year). Aspiration cytology seldom distinguishes follicular carcinoma from follicular adenoma[1,2]. A diagnosis of malignancy is dependent on the presence of capsular and/or angioinvasion which may be visible only at a single site. Meticulous histological examination of multiple paraffin blocks is therefore necessary to exclude a diagnosis of carcinoma in any follicular lesion.

DNA aneuploidy, which is a well recognized phenomenon in malignant disease, has been proposed as a possible marker for malignancy in follicular thyroid neoplasms[3–5].

To investigate this possibility the DNA ploidy of 12 follicular carcinomas and 30 follicular adenomas was examined in a retrospective flow cytometric study. In addition the DNA ploidy obtained from examination of paraffin-embedded tissue was compared prospectively with that found using fresh material from 23 additional follicular thyroid lesions.

Cell cycle analysis, in particular the proliferative index (i.e. the percentage of nuclei in the $S+G_2M$ phases of the cell cycle), may be of prognostic value in malignant tumours[6] and its possible diagnostic role as a discriminant in follicular neoplasia was examined.

Patients and methods

Twelve patients with a diagnosis of follicular carcinoma made between September 1982 and January 1985 were identified from pathology records. Haematoxylin and eosin (HE) sections from all available blocks were examined by one consultant pathologist (S.W.B.E.) and the diagnosis was confirmed in each case. Thirty patients with a diagnosis of follicular adenoma were identified from pathology records (September 1983 to February 1986) and HE sections examined from all available paraffin blocks to confirm the diagnosis.

Twenty-three patients with a follicular thyroid lesion (one carcinoma, 22 adenomas) were identified prospectively over a 9 month period October 1986 to June 1987. Fresh material was studied and paraffin sections were subsequently obtained.

Fixed tissue

A paraffin block containing the most aggressive area of tumour was selected after examination of contiguous HE sections from all available material. If large areas of normal thyroid tissue were present on the block these were masked when sections were taken. Preparations of single cell suspensions from paraffin embedded tissue were made using the method of Hedley *et al.*[7].

Fresh tissue

Surgical specimens were cut in the operating theatre and a portion of the lesion placed in normal saline. Fine needle aspiration was performed within 2 h to produce single cell suspensions. These were either snap-frozen in 1 ml aliquots and stored at −20°C or stored in 70 per cent alcohol at 4°C. The remainder of the specimen was processed for histopathology. Ten blocks, if possible, were routinely taken in a search for invasive features.

Flow cytometry

Staining was carried out using propidium iodide with modification of the detergent/trypsin method described by Vindelov *et al.*[8–10] and flow cytometric DNA analysis was carried out on an EPICS C flow cytometer[11] (Coulter Corp, Florida, USA). The coefficient of variation (CV) was measured in each case and a CV of greater than ten was considered unacceptable. With suspensions derived from paraffin embedded tissue the first major peak was assumed to represent DNA diploid nuclei[7]. Aneuploidy was defined as the presence of a second peak clearly distinct from the first population. In aneuploid tumours the DNA index was calculated from the ratio of the modal channel numbers. In fresh samples the specimens were run twice; once alone and once in the presence of control chicken and trout red blood cells. These controls allows calculation of the exact DNA ploidy from the relative peak channel positions[10,12]. Cell cycle analysis was performed using computer software (PARA 1, Coulter Corporation) on all tumours with a diploid DNA distribution pattern on flow cytometry.

Results

The results from all paraffin embedded material obtained either prospectively or retrospectively were considered together.

Follicular carcinoma

There were five females and eight males with median age of 42 years (range 12–76 years). Four (31 per cent) tumours showed DNA aneuploidy and nine showed a unimodal DNA profile. The mean CV of the diploid tumours was 8·1 (range 6·2–9·9). Cell-cycle analysis of diploid tumours showed a median proliferative index of 19 per cent (range 13–43 per cent). Cell cycle analysis was not possible in aneuploid tumours because of juxtaposition of the diploid and aneuploid peaks.

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A 68 year old patient with a DNA aneuploid tumour died within a month of operation from widespread metastatic disease A 33 year old patient with a diploid tumour died from proven metastatic breast carcinoma. The remaining 11 patients are alive and disease free 2–5 years after operation.

Follicular adenoma

There were 11 males and 41 females with a median age of 42·5 years (range 19–77 years). In seven cases the CV was greater than ten and these were excluded from further analysis. Of the remaining 45 tumours eight (18 per cent) were aneuploid and 37 were diploid; the mean CV was 7·7 (range 4·2–9·8).

Statistical analysis using Fisher's exact test showed no significant difference in the frequency of DNA aneuploidy between follicular adenoma and follicular carcinoma.

Cell cycle analysis of diploid tumours showed a median proliferative index of 27 per cent (range 15–51 per cent).

Comparison of fresh and paraffin embedded material

Data were available from both paraffin embedded and fresh tissue from 22 adenomas. Unsatisfactory results were obtained from the paraffin embedded material in four and, of the remaining 18, four (22 per cent) were DNA aneuploid. Examination of fresh material showed aneuploidy in six (27 per cent) of the 22 adenomas. Concordance was obtained in 13 diploid and three aneuploid tumours. One tumour was aneuploid on examination of paraffin-embedded material but diploid in fresh material and one tumour was diploid in paraffin-embedded material but aneuploid in fresh material. Of the four adenomas with unsatisfactory profiles on analysis of paraffin-embedded material two showed a diploid and two an aneuploid profile on analysis of fresh tissue.

Discussion

DNA aneuploidy in follicular thyroid lesions was first described in 1968 by Haemmerli[13] who showed in a static cytometric study that over 70 per cent of microfollicular lesions were aneuploid whereas histologically normal and macrofollicular lesions had a DNA content similar to control cells. The exact nature of the follicular lesions was not defined. In 1984 Bengtsson *et al.*[4] reported the results of static cytometric DNA analysis in a series of 94 thyroid imprints. A complex classification of histograms was used but the majority of benign lesions fell into one group and the majority of malignant lesions (with the exception of medullary carcinoma) into another. All eight follicular adenomas were in the 'benign' group and all six follicular carcinomas were in the 'malignant' group. It was suggested that DNA aneuploidy might distinguish benign from malignant thyroid lesions including follicular neoplasms. Rabenhorst[3] examined the DNA profiles of seven follicular adenomas with cellular atypia and found none to be aneuploid whereas two of three well differentiated carcinomas were aneuploid. He concluded that DNA aneuploidy was diagnostic of malignancy. This view was supported by Greenebaum *et al.*[5] using flow cytometry in a variety of thyroid lesions.

The overall results of the present study which showed the frequency of DNA aneuploidy in follicular adenomas to be 8 of 45 (18 per cent) are similar to those of a recent flow cytometric study of 67 tumours in which 27 per cent of follicular adenomas were aneuploid[14].

The finding that both follicular adenomas and follicular carcinomas may be either diploid or aneuploid makes DNA aneuploidy valueless in discriminating the one from the other. Cell cycle analysis was also unhelpful in distinguishing benign from malignant follicular neoplasms with no significant differences in the proliferative index.

The few published studies comparing ploidy in archival and fresh material have reported a close correlation[7,15,16] including the single comparative study carried out on thyroid tissue[14].

In the comparative part of this study there was disagreement between the results in fresh and paraffin-embedded material in two cases. Such discrepancy may be explained by failure to sample the same area of the specimen i.e. either the aspirate was not representative of the tumour or there was heteroploidy within the tumour[6]. Alternatively, inferior resolution in paraffin-embedded tissue may conceal cell sub-populations

Aneuploidy detected by quantitative static cytometry of archival material is highly accurate in predicting death from papillary thyroid carcinoma[17,18]. When detected by flow cytometry it is less accurate although still a discriminant[18] In follicular carcinoma DNA aneuploidy measured by either static cytometry[19] or flow cytometry[20] correlates with aggressive behaviour and poor prognosis. It has been proposed that DNA aneuploidy in differentiated thyroid carcinoma may not be an independent prognostic factor – the relationship resulting from a close correlation between age and aneuploidy[20]. We found no relationship, however, between age and DNA aneuploidy in patients with either follicular carcinoma or adenoma.

What is the clinical significance of aneuploidy in follicular neoplasms that are apparently benign on careful histology? Prognostic significance in malignant follicular neoplasms suggests that DNA aneuploidy in benign conditions may be a sinister feature. Whether patients are at risk of developing late metastases after excision of an aneuploid follicular adenoma is unknown. It is also unknown whether these lesions if not removed would eventually develop frankly malignant characteristics or whether DNA aneuploidy may simply be an aberration common to both benign and malignant neoplasms.

A diagnosis of follicular carcinoma depends upon meticulous histological examination for capsular or angioinvasion. The frequency of aneuploidy is similar in both 'adenoma' and 'carcinoma'. To distinguish these neoplasms categorically into benign and malignant types is unrealistic and probably biologically unsound. All follicular neoplasms are therefore best excised.

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Further evaluation of radical surgery following radiotherapy for advanced parotid carcinoma

N. C. Gallegos, G. Watkin, H. P. Cook, R. Sanders and M. Hobsley

Department of Surgery, University College and Middlesex School of Medicine, London WC1E 6JJ, UK

Correspondence to:
Professor M. Hobsley

A series of 30 patients who have been treated for advanced carcinoma of the parotid gland using radiotherapy followed by radical surgery is presented. Three patients deteriorated during preoperative radiotherapy and remained unfit for surgery; the remaining 27 underwent radical parotidectomy with block dissection of the neck. Twelve patients received additional radiotherapy after operation. Of those patients undergoing surgery, three have been lost to follow-up, 17 have died and seven remain alive; the period of follow-up ranges from 3 to 133 months. Fourteen patients remained free of recurrent disease at death or when last seen, and six patients developed a local recurrence at a median period of 10·5 (range 3–36) months after surgery. For all 30 patients, the cumulative proportion surviving for 5 years was 30 per cent.

The principal objective in the management of parotid carcinomas is to gain complete control of the primary tumour. Attainment of this goal not only spares the patient the distress of recurrent local disease but also reduces the risk of developing metastases and may increase survival[1,2].

The efficacy of combined treatment involving surgery followed by radiotherapy is now well recognized in the management of parotid malignancies[1,3,4]. However, while the majority of parotid carcinomas present at a relatively early stage and are amenable to surgical resection, difficulties arise with advanced tumours when size or invasion of adjacent structures renders them inoperable. These cases usually receive palliative treatment in the form of radiotherapy, although this approach is unsatisfactory because adequate control is gained in less than 50 per cent of cases[2,5,6].

While radiotherapy alone generally provides poor palliation, parotid carcinomas are radiosensitive with up to 84 per cent of cases showing complete or partial regression[7]. It follows that radiotherapy may be used to reduce tumour bulk and render inoperable cancers amenable to surgical excision[8,9].

We have previously described the use of radiotherapy followed by surgery to control locally advanced parotid carcinomas[9]; this approach was successful in containing the primary tumour in nine of 12 cases. Encouraged by these results, our experience has been extended and we now present an analysis of 30 patients with advanced parotid tumours (including the original 12) who have undergone this mode of treatment.

Patients and methods

In this series the term advanced carcinoma of the parotid gland was applied to those tumours which fulfilled the criteria for stage III or IV disease as described in the tumour node metastasis (TNM) classification proposed by Levitt *et al.*[10]. Such tumours are either greater than 6 cm in diameter or, regardless of size, have spread to involve the regional lymph nodes or at least two adjacent structures such as the facial nerve or mandible. All tumours in this series were considered unsuitable for surgical resection alone, either because of size or their fixation to the surrounding tissues, to attempt operation under these conditions would have inevitably left macroscopic disease behind and might even have had an adverse effect by spreading tumour along disturbed tissue planes.

The details of all patients referred to the Middlesex Hospital with salivary gland disease are recorded on a prospectively maintained database. The records of patients presenting with parotid carcinomas were retrieved and those cases involving advanced tumours selected for further study. Since these patients are referred from all over the country, follow-up was sometimes difficult. In some instances treatment was initiated by us and continued at the referring hospital. Where records were incomplete, the centre of referral was contacted for further information. Of the 30 patients presented here, three were lost to follow-up although in each case the patient had already developed locally recurrent disease when last seen.

Between September 1972 and December 1986, 42 patients with advanced carcinoma of the parotid gland were referred to the Middlesex Hospital under the care of one surgeon (M.H.) and one radiotherapy department. Of these, 12 were excluded from receiving radical treatment because of the presence of distant metastases. Of the remaining 30 patients (median age 60·5, range 28–78 years), there were 19 men and 11 women. Nineteen patients fulfilled the criteria for stage III disease and 11 for stage IV disease. Seven patients were referred with recurrent disease: five had previously undergone operation combined with radiotherapy and two had been treated with operation alone.

The median size of the tumours at presentation was 5 cm (range 2–12 cm), and the pattern of physical signs was as shown in *Figure 1*. Where histological confirmation of the diagnosis was not available from the referring centre an open biopsy was performed. A list of the different histological types of malignancy encountered in the series is provided in *Table 1*, apart from the adenoid cystic carcinomas, all were high grade tumours and were considered to carry a poor prognosis regardless of their stage at presentation. Routine investigations before treatment included plain radiographs of the skull and mandible to exclude a primary bone tumour and, in the latter half of the series, a computed tomography scan was performed as an aid to radiotherapy field planning.

Two-thirds of the planned total dose of radiotherapy was administered before operation, the remaining third being held in reserve for those patients with incomplete removal of the tumour or aggressive carcinomas. This policy was adopted to minimize the complications associated with operating on irradiated tissues while still achieving a worthwhile reduction in tumour bulk.

Twenty-six patients received preoperative radiotherapy. This was given to a mean total dose of 4000 (range 2600–6500) cGy; four patients did not undergo this treatment because the dose of radiation administered before referral precluded it. On completion of radiotherapy, three patients were considered unsuitable for major surgery, in two of these, distant metastases had developed and in the third patient a large tumour (6 cm in diameter) had not responded sufficiently to allow surgical excision to be contemplated.

Therefore, of the original 30 patients, 27 proceeded to operation which was carried out in conjunction with an oral and a plastic surgeon. All patients underwent a radical parotidectomy with sacrifice of the facial nerve together with *en bloc* excision of the overlying skin, including the pinna where necessary, and resection of all or part of the hemimandible and zygoma as required. In addition and in

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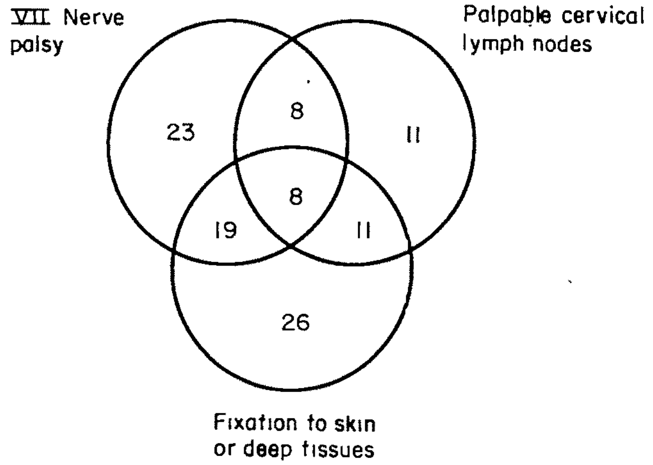

Figure 1 *Distribution of physical signs*

Table 1 *Histological types of tumour*

Histology	No of patients
Adenoid cystic carcinoma	5
Carcinoma ex-pleomorphic adenoma	5
Adenocarcinoma	4
Squamous cell carcinoma	7
Mucoepidermoid tumour	2
Undifferentiated carcinoma	6
Carcinoma ex-monomorphic adenoma	1
Total	30

continuity with the above, a block dissection of the neck was performed to remove the regional lymphatic drainage. Closure of the resulting defect was accomplished by means of rotation skin flaps or myocutaneous flaps fashioned either as pedicled grafts (nine cases) or as free flaps (two cases). Where appropriate, the facial asymmetry caused by division of the seventh nerve was corrected by means of a fascia lata sling to support the angle of the mouth, and either a gold weight inserted into the upper eyelid or a delayed lateral tarsorrhaphy performed to assist closure of the palpebral fissure

Twelve patients received postoperative radiotherapy (mean total dose 2640 cGy, range 1500–4500 cGy), the need for which was dictated by the presence of microscopic disease at the resection margins, the surgeons' impression of tumour clearance at the time of operation, and the histology of the tumour

Statistical analysis was by means of Fisher's exact test, and the cumulative survival rates for all 30 patients were calculated according to the method of Kaplan and Meier[11].

Results

The 26 patients who received preoperative radiotherapy all obtained a reduction in the size of their tumour. However, in one case, where a large carcinoma had infiltrated the ascending ramus of the mandible and the base of the skull, the response was insufficient to allow surgery to take place, a further two patients were excluded from proceeding to a radical parotidectomy because of the interim appearance of metastatic disease.

There was no immediate postoperative death as judged by its occurrence within 30 days of surgery, and the main complications seen related to the extensive nature of the wound and its closure. Eight patients developed a wound infection and in two this was associated with breakdown of the covering skin which was severe enough in one case to require grafting. One patient, who received a free flap to provide wound closure, suffered necrosis of the graft secondary to the formation of a haematoma; this resulted in an extensive defect which was eventually closed using a free latissimus dorsi flap from the contralateral side. Two patients developed an orocutaneous fistula which required operative closure, and one patient required insertion of a grommet for a secretory otitis media.

In 20 patients (74 per cent), complete histological clearance of the tumour was obtained, and in 14 of these there was no evidence of regional lymphatic spread. Nine patients had lymph node metastases confirmed, but in only five cases was this finding suspected before operation.

Twelve patients received postoperative radiotherapy. This was given to five of the seven patients who had histologically involved resection margins, and to seven other patients because of the aggressive nature of the original tumour. Two patients with involved resection margins were not irradiated. In one this was because a full dose of radiotherapy had been received prior to referral and in the other the patient had an adenoid cystic carcinoma which was considered insufficiently aggressive to warrant further treatment.

Over a variable period of time (median 35·5 months, range 3–133 months) 17 patients have died, seven remain alive and three have been lost to follow up. A total of 13 patients developed further disease; in six this manifested as local recurrence of the tumour at a median time of 10·5 (range 3–36) months, and in three was associated with the synchronous appearance of distant metastases. The details of those patients who suffered local recurrence, defined here as the reappearance of tumour above the level of the clavicle, are given in *Table 2*. It can be seen that five of the six local recurrences occurred in patients in whom clear resection margins were present, and that only one of these six patients had received postoperative radiotherapy; in other words, five local recurrences were observed in the 15 patients who did not receive postoperative radiotherapy. In contrast to this, only one of 12 patients who received postoperative radiotherapy relapsed locally despite five having involved resection margins. There was no difference in the incidence of local recurrence between those patients who had histological evidence of lymph node metastases (two of nine patients) and those who did not (four of 18 patients). Of the five patients who had received surgery and radiotherapy prior to referral, three developed local recurrences (*Table 3*).

Of the histological types of tumour in this series, four of the five patients with adenoid cystic carcinomas did particularly well; none developed local recurrence and all died of unrelated disease at a median time of 28 (range 24–105) months. The tumour of the fifth patient remained inoperable following radiotherapy.

The survival curve for the 30 patients in this series is shown in *Figure 2*. The cumulative proportion surviving for 5 years was 30 per cent.

Discussion

Carcinomas and mucoepidermoid tumours account for about 15 per cent of all parotid tumours[12], and of these less than half can be expected to present with advanced disease as defined above[10]. In late presentations there may be extensive involvement of contiguous structures which renders methods of local control, either by surgery or radiotherapy, ineffective.

With one exception, all the tumours in our series responded sufficiently to radiotherapy for subsequent parotidectomy to be feasible, although a further two patients had to be excluded from surgery because of the appearance of distant metastases. Of the 27 patients who underwent surgery, 20 (74 per cent) had clear resection margins and only six patients developed locally recurrent disease. This result compares favourably with other reported series in which 'inoperable' tumours have been treated by conventional radiotherapy alone (*Table 4*).

Comparable results have been achieved using fast neutron therapy with local control rates of 55 per cent[13] and 80 per cent[14] recorded for patients with inoperable tumours arising in the major salivary glands. However, direct comparison with our series is difficult; not all the patients treated had parotid tumours and the reasons for deciding they were inoperable were not specified. Furthermore, 26 of the

Table 2 *Details of patients with recurrent local disease*

Case no	Histology	Resection margin clear	Postoperative radiotherapy	Site of recurrence	Interval (months)
1	Carcinoma ex-pleomorphic adenoma	Yes	No	Maxillary antrum	36
2	Carcinoma ex-pleomorphic adenoma	Yes	No	Mandible	9
3	Undifferentiated carcinoma	Yes	No	Skin flap	3
4	Undifferentiated carcinoma	Yes	Yes	Maxillary antrum	9
5	Mucoepidermoid tumour	No	No	Skin flap	14
6	Squamous cell carcinoma	Yes	No	Mandible	9

Table 3 *Details of patients referred for the treatment of recurrent disease following radiotherapy and/or surgery*

Histology	Previous treatment	Local recurrence	Time (months)	Treatment	Outcome (months)
Carcinoma ex-pleomorphic adenoma	Surgery and radiotherapy	Yes	36	Chemotherapy and radiotherapy	Alive (60)
Carcinoma ex-pleomorphic adenoma	Surgery and radiotherapy	Yes	9	Chemotherapy	Lost to follow-up
Adenocarcinoma	Surgery and radiotherapy	No	–		Dead with pulmonary metastases (45)
Undifferentiated carcinoma	Surgery and radiotherapy	No	–		Dead with chest wall metastases (8)
Mucoepidermoid tumour	Surgery and radiotherapy	Yes	14	Surgery and radiotherapy	Alive with local recurrence (17)
Adenoid cystic carcinoma	Surgery	No	–		Alive (56)
Squamous cell carcinoma	Surgery	No	–		Alive (3)

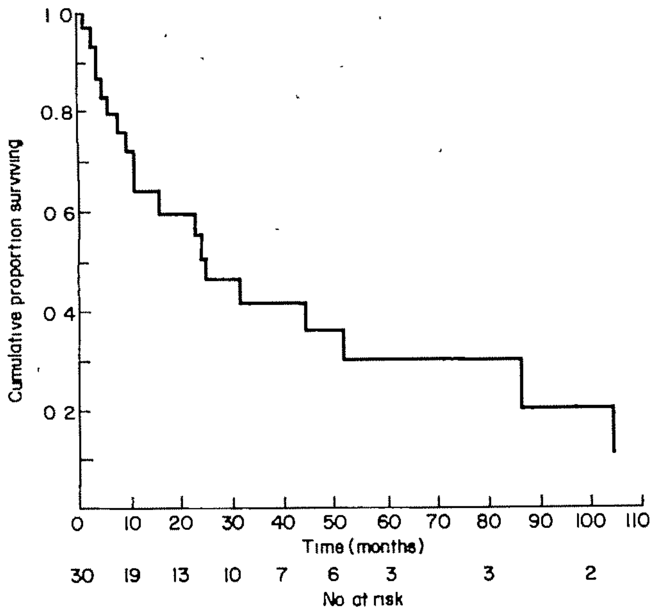

Figure 2 *Cumulative proportional survival for all patients*

Table 4 *Local control of inoperable salivary gland tumours using external beam radiotherapy*

	No. of patients with inoperable tumours	Local disease control *n*
Byun *et al.*[2]	23	5 (22)
Shidnia *et al.*[5]	10	0
Theriault *et al*[6].	33	6 (18)
King *et al.*[25]	16	11 (69)
Rampling *et al* [14]	56	45 (80)*

Values in parentheses are percentages. * Patients treated with fast neutron therapy

reported 56 cases were adenoid cystic carcinomas which, while recognized as having a propensity to recur locally, nevertheless have a good prognosis compared with the majority of tumours in our series. There is also evidence to suggest that fast neutron therapy is ineffective against carcinomas larger than 6 cm[15]. In our series, five patients had tumours greater than 6 cm and, although all of these patients are now dead, three died without local recurrence.

Extensive surgery in an irradiated field is likely to produce complications. Compromised tissues and breaches of the buccal mucosa predispose to wound infections, which occurred in eight patients despite the use of prophylactic antibiotics. There was no postoperative death but three patients suffered serious complications: two orocutaneous fistulae formed and each required several operations to achieve closure; and one patient required reoperation for necrosis of a free flap graft. However, the alternative treatment of radical radiotherapy is also not without serious complications, including transverse myelopathy, meningitis and osteoradionecrosis[16,17].

Although the difference in incidence of locally recurrent disease between those who received postoperative radiotherapy (one of 12 patients) and those who did not (five of 15 patients) failed to reach statistical significance ($P>0.05$, Fisher's exact test), we believe that all patients, regardless of the adequacy of tumour clearance, should complete a full course of radiotherapy where possible.

The place of radical neck dissection in the management of parotid carcinomas remains controversial. Despite evidence to suggest that the recurrence rate for neck disease is the same whether the lymph nodes are removed prophylactically or for established disease[18,19], we believe, as do others[20], that the best way of reducing cervical recurrence in patients with advanced tumours is to perform a block dissection of the neck. This policy maximizes the chances of removing all gross disease and, with the addition of either preoperative or postoperative radiotherapy, has been shown to reduce the local failure rate below that of surgery alone[21,22]. With this radical approach none of our patients developed a recurrence in the dissected neck. However, the presence of lymph node metastases had no influence on recurrence at the primary site.

Of the seven patients referred to us for treatment of recurrent disease, five had received a combination of surgery and radiotherapy and of these, three subsequently developed further local recurrences. This high failure rate, coupled with the relatively poor prognosis associated with local relapse[23], suggests that the radical treatment employed here is unsuitable for recurrent cancers and that palliative radiotherapy, chemotherapy or the recently described technique of ^{125}iodine endocurietherapy[24] should be used instead.

It is difficult to compare our 5-year cumulative survival rate of 30 per cent with the rates reported by other authors. This is partly due to the heterogeneous nature of the patients in our series, comprising as they do both stage III and stage IV disease, and partly to the relatively few cases of advanced inoperable parotid carcinomas which are available for study in the literature. Consequently, we cannot say whether our treatment has conferred a survival advantage on the patients treated, but our results compare favourably with the limited information available; thus the reported 5-year survival rate for stage III disease is 43 per cent and for stage IV disease it is 8·5 per cent[10], while 5-year survival rates ranging from 0 to 30 per cent are recorded for patients whose tumours were treated by radiotherapy alone[3,25].

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Double-blind randomized trial of perioperative fibrinolytic enhancement for femoropopliteal bypass

D. C. Berridge, M. Frier, J. C. Westby, B. R. Hopkinson and G. S. Makin

Department of Vascular Surgery, University Hospital, Nottingham, UK

Correspondence to:
Mr D. C Berridge,
Middlesborough General Hospital,
Ayresome Green Lane,
Middlesborough TS5 5AZ, UK

Patients with rest pain or acute peripheral arterial thrombosis are known to have impaired endogenous fibrinolysis, which is associated with an increased risk of early vascular graft thrombosis. This risk is exacerbated by the fibrinolytic shutdown which is known to occur after major surgery. Stanozolol, which has been demonstrated to enhance endogenous fibrinolysis, was therefore used in an attempt to prevent this perioperative fibrinolytic shutdown and so enhance graft patency. Twenty-seven patients were randomized to receive either 50 mg stanozolol or placebo intramuscularly 24 h before operation, followed by a 6 week course of either 5 mg stanozolol or placebo orally, twice daily. On the second day after operation, 10–11 MBq of autologous ^{111}indium-labelled platelets were injected, with scanning over the graft on the 3 following days. Despite using a large depot of stanozolol, significant effects, such as raised plasminogen ($P<0{\cdot}001$), reduced fibrinogen ($P<0{\cdot}001$) and reduced euglobulin lysis time ($P<0{\cdot}001$), were not seen until the seventh day after operation, with maximum benefit at 6 weeks. This was reflected in the ^{111}indium-labelled platelet deposition studies. The placebo group had a progressive increase in platelet deposition on all 3 days. In contrast, those receiving stanozolol showed a lower, static picture of deposition. However, these changes did not attain statistical significance. Three patients experienced early graft thrombosis, two in the placebo group and one in the stanozolol group. Only an incomplete inhibition of the perioperative fibrinolytic shutdown was achieved. Much longer preoperative courses are thus required to allow the maximum effect to be present at the most crucial time. At present, perioperative fibrinolytic enhancement does not appear to be a practical proposition, and we must await the development of new safer and more potent agents.

Several studies have suggested an important role for endogenous fibrinolysis in maintaining the patency of aortocoronary[1], and infrainguinal saphenous vein bypass grafts[2,3]. Recently, Earnshaw *et al.*[4] demonstrated that a reduced fibrinolytic potential is associated with a significantly higher risk of graft failure, and that patients with rest pain and those with acute thromboses had a significantly higher euglobulin lysis time before and after occlusion than either normal controls or patients with intermittent claudication Furthermore they demonstrated that patients with a reduced fibrinolytic potential were more likely to incur early graft thrombosis. This effect is compatible with the fibrinolytic shutdown which is known to occur after major surgery[5]. In the pursuit of improved results for femoropopliteal and particularly femorodistal bypass surgery, correction of this fibrinolytic deficit may be worthwhile.

Drugs capable of enhancing endogenous fibrinolysis are already available. Pentoxifylline, which also has important effects on red cell deformability and plasma viscosity, has been shown to be superior to the combination of aspirin and dipyridamole in the prevention of femoropopliteal graft thrombosis[6] This effect is thought to be due to its ability to enhance endogenous fibrinolytic activity. Stanozolol has also been demonstrated to enhance endogenous fibrinolysis in both normal subjects and patients[7–9] In brief, the plasminogen level is raised, the fibrinogen level is lowered and the euglobulin lysis time is reduced. The reduction in euglobulin lysis time (i.e the potentiation of fibrinolysis) can be maintained for over 5 years with a maintenance stanozolol dose of 5 mg per day, although the development of resistance has occasionally been reported[10]. Using oral therapy, at least 2 weeks are necessary to achieve a significant enhancement of fibrinolysis[11]. This is impractical in the context of perioperative fibrinolytic enhancement. However, an intramuscular depot injection of 50 mg produces an increase in tissue plasminogen activator activity after 24 h which is greater than that produced by 2 weeks of oral therapy. A randomized, double-blind controlled trial of perioperative fibrinolytic enhancement for femoropopliteal bypass has been performed using this intramuscular dose

Patients and methods

It was intended to recruit 30 patients due to undergo femoropopliteal bypass Patients with a history of liver disease and those receiving high-dose diuretic therapy or digoxin were excluded Clinical examination, including Doppler ankle artery pressure studies, were performed at each assessment period and blood was taken to estimate haemoglobin, urea and electrolytes, liver function tests, plasminogen, fibrinogen and euglobulin lysis times at each assessment period

Euglobulin lysis time was assessed using a modification of the method of Buckell[12]. Venous blood was obtained with a minimum of

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venous stasis and placed in 0·106 M trisodium citrate dihydrate. The sample was placed in ice and transferred immediately to the coagulation laboratory where it was centrifuged and either tested immediately or stored at −70°C for analysis in batches at a later date. Fibrinogen samples were analysed by the method of von Clauss[13]. Venous blood was collected into 10 per cent aprotinin in 0·106 M trisodium citrate and stored as above. Plasminogen was estimated with a synthetic chromogenic substrate using a commercial kit (Behring Diagnostics, Hounslow, UK). Venous blood was placed in citrate as above, separated, and stored at −70°C for testing in batches.

Patients were then randomized to receive either 50 mg stanozolol or placebo intramuscularly, 24 h before operation. Starting on the second day after operation, patients received a 6 week course of either 5 mg stanozolol twice daily or a placebo tablet twice daily.

On the second day after operation, 26 ml venous blood were obtained using no or minimal tourniquet time. Platelets were prepared and labelled by the method of Hawker *et al.*[14] ^{111}Indium oxine labelling was performed in plasma free medium and cells were out of contact with plasma for less than 1 min. Patients received 10–11 MBq of autologous ^{111}indium-labelled platelets.

Imaging was performed on three consecutive days using a large field of view IGE400AC γ-camera (IGE Medical Systems Ltd., Slough, UK) fitted with medium energy collimator (300 keV) and energy windows centred on both photopeaks of ^{111}indium (173, 247 keV). To assist in the positioning of the regions of interest, radioactive markers were placed alongside the limb. These consisted of four point sources each containing 3·7 MBq ^{57}cobalt placed at approximately 18 cm intervals along the length of a perspex strip. Each field of view included two markers and overlapping views were recorded such that the lower marker from the previous view became the upper marker of the current view. The uppermost marker was placed adjacent to the anterior superior iliac spine, and could be clearly identified on the ^{111}indium platelet image.

Assessment was made before operation, at 2 and 7 days after operation, and at 6 (end of treatment) and 10 weeks after operation. Any doubts about graft patency were resolved using an intravenous digital subtraction angiogram.

All patients gave fully informed consent. This study was approved by the Medical Ethical Committee of the University Hospital, Nottingham. All statistics were performed using the χ^2 or Mann–Whitney *U* test as appropriate on an ICL3900 mainframe computer (ICL Computers, Manchester, UK) using the MINITAB program (Minitab Corporation, USA).

Results

Recruitment was stopped after 27 patients had been entered, because statutory changes limited provision of further drug supplies by the manufacturer. Results of clinical follow-up and fibrinolytic, biochemical and scintigraphic investigations were obtained before randomization code was broken.

There were no significant differences between the stanozolol and placebo groups in terms of age, ankle artery pressure, ankle/brachial pressure index or run-off (*Table 1*). No patient died and no amputations were required during the follow-up period of 10 weeks, despite occlusion of three grafts.

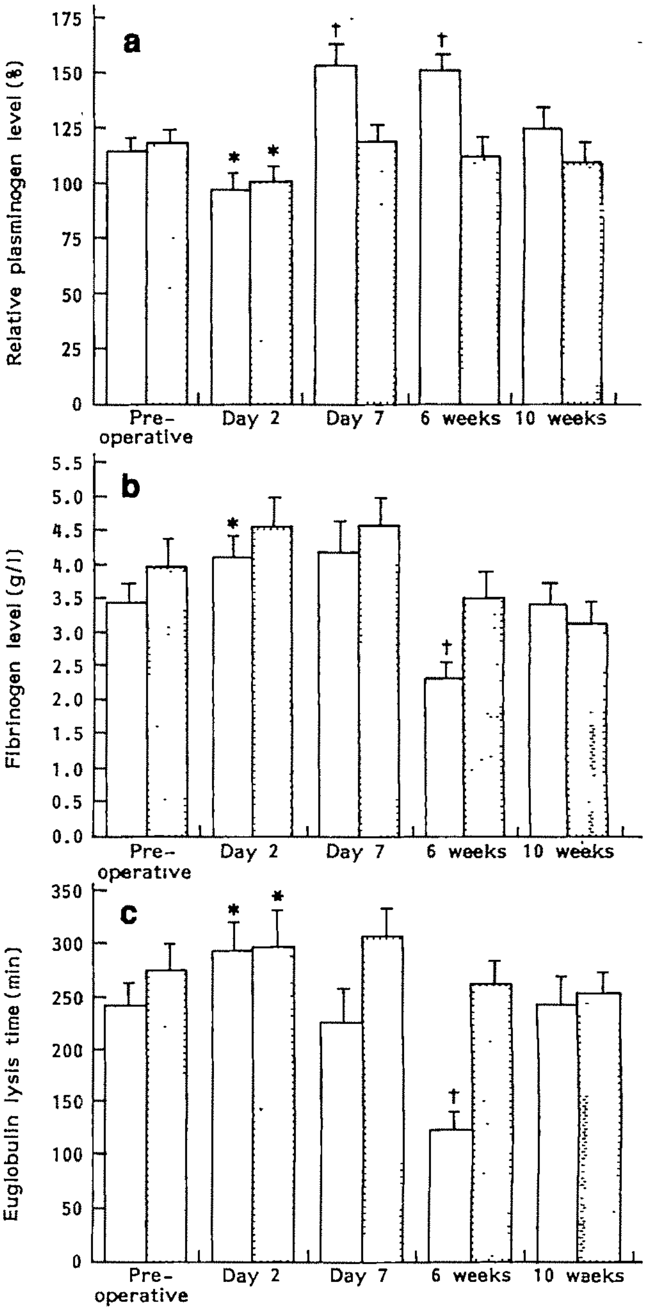

Figure 1 *Effects of stanozolol* (□) *and placebo* (▨) *on* **a** *plasminogen*, **b** *fibrinogen and* **c** *euglobulin lysis time.. Compared with initial values,* *P<*0·05,* †P<*0·001*

Table 1 *Patient details*

	Placebo group (*n* = 13)	Stanozolol group (*n* = 14)
Mean age in years (s.d.)	67(8)	65(7)
Median ankle pressure in mmHg (interquartile range)	35(0–49)	32(0–52)
Median ankle/brachial pressure index (interquartile range)	0·22(0–0·34)	0·24(0–0·42)
No. of calf run-off vessels	2	2
No. with elevated liver enzymes*	8†	8‡
No. of grafts with early thrombosis	2	1

* Alkaline phosphatase, alanine aminotransferase, γ-glutamyl transferase; † 6 reversible, 2 non-reversible; ‡ 8 reversible

Fibrinolytic parameters

Plasminogen (Figure 1a). In both groups a significant reduction in plasminogen occurred at day 2 ($P < 0·05$), but was soon followed by a significantly elevated level from day 7 which continued throughout the treatment period in the stanozolol group ($P < 0·001$). The placebo group returned to initial levels. There were no significant differences between the placebo and the stanozolol groups in the initial or day 2 samples. The elevated levels in the stanozolol group were significantly higher than the corresponding level in the placebo group. Both groups had returned to their initial values at the time of the final sample, taken 4 weeks after the treatment had finished.

Fibrinogen (Figure 1b). In the placebo group, there was a small but non-significant increase in fibrinogen level during the course of therapy (placebo tablets), which was not present in the final sample 4 weeks after the treatment period had finished.

In the stanozolol group, however, the same rise was seen but reached statistical significance ($P < 0\cdot05$). At the end of the 6 weeks this had completely reversed and the stanozolol group now showed a significant reduction in fibrinogen level to 2·3 (range 2–2·8) g/l, compared with both the initial level and also the corresponding level in the control group ($P < 0\cdot001$).

Euglobulin lysis time (Figure 1c). In both groups euglobulin lysis time showed an initial rise ($P < 0\cdot05$) consistent with a significant reduction in resting fibrinolytic activity – the so-called 'perioperative fibrinolytic shutdown'. The stanozolol group then showed a significant reduction in euglobulin lysis time reaching a level of 130 (range 99–146) min ($P < 0\cdot001$) at 6 weeks.

^{111}Indium-oxine platelet deposition

Platelet deposition was quantified and corrected for background radiation in the defined regions of interest. The results were expressed as a ratio compared with mirror image regions on the contralateral limb:

$$\text{Thrombogenicity ratio} = \frac{\text{actual count} - \text{background count (graft)}}{\text{actual count} - \text{background count (contralateral limb)}}$$

Thrombogenicity ratios were calculated for both proximal and distal anastomoses, and for the body of the graft. Due to the low dose of radioactivity administered, count rates were generally low. In the placebo group there was a significantly higher thrombogenicity ratio at the lower anastomotic site compared with the rest of the graft ($P < 0\cdot05$) on day 1. Although the ratios increased in all zones up to and including day 3, such increases did not attain statistical significance (*Table 2*). Conversely the stanozolol group showed a lower, static, uniform platelet deposition throughout the study.

Discussion

Patients with arteriosclerosis of the lower limbs are known to have an impaired fibrinolytic capacity which is dependent on the severity of the ischaemia[15]. They have been shown to have a significantly reduced resting and potential fibrinolytic activity compared with normal controls. In comparison with the upper limbs, fibrinolytic activity in the lower limbs is reduced, and is exacerbated by ischaemia. Robertson *et al.*[6] demonstrated a fourfold greater fibrinolytic activity in venous blood from the arm following a 20 min period of occlusion at a level midway between systolic and diastolic. This difference was ascribed to chronic hydrostatic pressure depleting the local vasculature of plasminogen activator. Karaca and Nilsson[17] found that hemiplegic patients confined to bed for a long time had almost the same fibrinolytic activity in the legs as in the arms.

Table 2 *Thrombogenicity ratios over three consecutive days at the upper anastomoses, the middle of the graft and the lower anastomosis, in placebo and stanozolol treated patients*

	Placebo group ($n = 13$)	Stanozolol group ($n = 14$)
Day 1		
Upper	1·23(1·03–1·68)	1·26(1·06–1·70)
Middle	1·01(0·6–1·43)	1·13(0·95–1·84)
Low	1·34(1·15–2·33)	1·13(0·81–1·84)
Day 2		
Upper	1·38(1·17–1·94)	1·31(0·78–1·58)
Middle	1·44(0·96–1·75)	0·90(0·01–1·66)
Low	2·01(1·41–3·88)	1·33(1·2–3·32)
Day 3		
Upper	1·66(1·34–2·17)	1·06(1·45–2·39)
Middle	1·94(0·99–4·66)	1·1(1·17–2·94)
Low	1·95(0·83–3·08)	1·0(0·65–2·86)

Values are median(interquartile range)

Impairment of endogenous fibrinolysis has been associated with early graft failure[2,4]. It would seem logical therefore that enhancement of this activity to normal or supranormal levels should have a beneficial effect. Despite using a 50 mg intramuscular preparation of stanozolol, the early fibrinolytic shutdown after operation was not eliminated in this study. A significant potentiation of enhancement occurred between 2 and 7 days after operation. This is disappointing in view of earlier work which demonstrated that a 50 mg depot of intramuscular stanozolol could supersede the maximum effect achieved by 2 weeks of oral therapy[11,18,19]. A single 50 mg stanozolol injection caused a 30 per cent elevation of endogenous fibrinolysis for the first week, followed by 15 per cent for 3 subsequent weeks[19]. The mode of action appears to be multifactorial with an increase in factor VIII and plasminogen activator levels[20]; hepatic enzyme induction is a prominent factor.

^{111}Indium-labelled platelet deposition in this study was generally low in all patients. Nevertheless a higher rate of platelet deposition was seen in the placebo group than in the stanozolol group throughout the study; this did not achieve statistical significance. A significantly higher thrombogenicity ratio was seen at the lower anastomosis compared with the rest of the graft in the placebo group and it may be that stanozolol did produce an enhancement of endogenous fibrinolytic activity. Although in terms of euglobulin lysis time this is not evident until 2 days after operation it is, nevertheless, associated with a reduced platelet deposition on days 2 to 4.

While short term therapy with stanozolol is relatively safe, long-term treatment is associated with hirsutism, acne, mental disturbance, transient increases in liver enzymes and, rarely, liver tumours[21]. Such anabolic steroids can also potentiate warfarin therapy[22]. The serious potential side effects of stanozolol make it a less than ideal drug for long-term use.

Nevertheless, this study illustrates the logistic problems of using fibrinolytic enhancers which may need to be given well before the time of operation to achieve their maximum effect. The ideal agent would achieve this effect within 24 h, have a prolonged half-life, and be free of androgenic side effects. The development of new, safer, more potent agents must occur before perioperative fibrinolytic enhancement becomes a viable proposition.

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Role of phenytoin in healing of large abscess cavities

S. C. Lodha,
M. L. Lohiya,
M. C. R. Vyas,
Sudha Bhandari,
R. R. Goyal and
M. K. Harsh

Department of Surgery, Dr S. N. Medical College, Jodhpur, Rajasthan, India
Correspondence to:
S C. Lodha

The promotion of healing of large abscess cavities attained with topical phenytoin was evaluated in controlled studies of clinical and experimental wounds. In the clinical abscess cavities, phenytoin application in 20 patients compared with conventional treatment in 20 patients resulted in earlier separation of slough, decrease in oedema, control of pain and overall enhanced healing. The mean(s.d.) rate of reduction of wound area was 2·02(0·48) cm^2/day in the phenytoin group versus *1·58(0·51) cm^2/day in controls* ($P<0·05$) *on day 10, and 1·8(0·32) cm^2/day* versus *1·19(0·21) cm^2/day* ($P<0·01$) *on day 20. The mean volume reduction rates at both the 10th and 20th day were 0·48(0·01) cm^3/day for phenytoin* versus *0·32(0·04) cm^3/day for controls;* ($P<0·005$). *By day 20, 17 of the patients treated with phenytoin were rated as having healed completely, compared with only one of the controls. In a standardized guinea-pig model of the clinical abscess cavity, which included inoculation of the wound with* Bacillus proteus *and* Klebsiella pneumoniae, *an enhanced healing rate was also observed (at 7 days 0·40(0·05) cm^2/day with phenytoin* versus *0·21(0·08) cm^2/day in controls;* $P<0·005$). *All eight of the animals treated with phenytoin healed by day 21, compared with one of the eight controls. Biopsies of wounds treated with phenytoin showed less inflammation, no necrosis, and enhanced neovascularization, collagen deposition and fibroblast proliferation compared to controls. Bacterial colonies also decreased more rapidly with the use of phenytoin.*

The history of wound healing is as old as the history of humankind. As early as 500–300 BC, Sushruta, the Indian surgeon, described 'Ropnam', meaning promotion of healing and reparative function, 'Bhrimhanan' meaning tissue building and 'Vaikrita', the pathological state in which 'Ropnam' and 'Bhrimhanan' do not function as they should[1]. Although the mechanisms of wound healing have been extensively studied since the time of Sushruta, available treatment methods, ranging from simple rest and elevation to manipulation of immune function and the local wound environment by providing growth factors, are far from satisfactory. Some may actually retard healing[2].

Abscess cavities are an extremely common problem in surgical clinics in India. Abscesses are most frequently secondary to injections involving improper sterile technique and/or the use of contaminated needles or syringes. Breast abscesses are also very common. Incision and drainage, together with systemic and local antibiotics, are necessary elements of the treatment of these abscesses. However, the resultant cavity is slow to heal and a cause of prolonged morbidity.

Phenytoin (diphenylhydantoin), best known as an anti-seizure medication in clinical use since 1938, has been reported to promote wound healing. In 1939, Kimball[3] first observed that gingival hyperplasia was treated in some epileptics with phenytoin, and this stimulated the use of phenytoin in wound healing. Shapiro carried out the first controlled clinical trial in 1958, finding that periodontal patients with surgical wounds who were pretreated with oral phenytoin had less inflammation, less pain and accelerated healing compared with controls[4]. Other investigators have extended the use of phenytoin in wound healing to topical treatment of periodontal disease and chronic ulcers of varying aetiology, as well as second degree burns[5–17].

The present controlled study was undertaken to evaluate the effects of topical phenytoin in the treatment of large abscess cavities. The observations reported here are based on a clinical series of 40 patients and data from 16 experimental wounds in a guinea-pig model.

Materials and methods

Clinical study

Forty consecutive patients with abscess secondary to intramuscular injections in the gluteal region were selected for this study and assigned randomly to either the phenytoin or control group. Neither age, sex, anaemia, nutritional status nor underlying systemic disease were considered in the initial selection process.

Before phenytoin or control therapy, all patients had incision and drainage of their abscesses. Antibiotics were given as appropriate to control residual infection, but all patients had ceased antibiotics at the time of entry into this trial. Twenty patients were treated with topical phenytoin and a dry dressing. The 20 control cases were first treated with 15 per cent Eusol. The cavities were then washed with 4 per cent urea and dressed with 0·9 per cent saline The mean(s.d) wound area in the group treated with phenytoin was 37·8 cm^2(8·5) and was 37·1 cm^2(8·5) in the control group. The mean(s.d.) wound volume in the group treated with phenytoin was 12·5(4·5), and was 10·7(1·9) in the control group. The mean duration of abscesses before incision and drainage was also comparable for both groups

Phenytoin-sodium power (Puneet International, Bombay, India) was delivered topically in a fixed dose of 20 mg/cm^2 by making a series of 25 perforations in a 5 × 5 grid over a 1 cm^2 area on the bottle cap To standardize dosage, the powder was tapped from a fixed distance onto a piece of paper, and the area covered was measured and weighed. Each tap of the bottle yielded 4 mg of phenytoin-sodium.

Dressings were changed and topical agents were applied daily for a maximum of 30 days in each group. All patients in both groups were given multivitamins with trace elements as supportive therapy No other therapeutic agents were used.

On the day of the first dressing, measurement of the area of each cavity was made by direct tracing of the outline of the wound on butter

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(wax) paper and then transferring it to graph paper In addition, the volume of each cavity was measured by instilling saline The presence or absence of pain was ascertained initially and at each dressing change during therapy

Every 10th day, the wound was assessed clinically for oedema of its margins and surrounding skin, presence of slough and/or discharge, appearance of healthy granulation tissue, appearance of growing epithelium at the wound margin, wound contraction, and reduction of wound area and volume. Each of these parameters was assessed on a scale of: −, none, ±, almost none, +, mild; + +, moderate; and + + +, marked

An overall clinical assessment of the wound was made every 10th day according to the following scale A, no healing; B, less than 25 per cent healing; C, less than 50 per cent healing; D, healing greater than 50 per cent, but less than 90 per cent; and E, nearly complete or complete healing (90–100 per cent). All assessments were made by the same physician Photographs (at a fixed distance from the wound) were also taken at baseline and every 10th day thereafter.

Experimental study

In the study of the effects of topical phenytoin on healing of standard, infected experimental wounds, eight guinea-pigs treated with phenytoin and eight control animals were evaluated. The animals were matched by age and weight and kept under the same conditions

A clean surgical incision (3·5 cm in length and extending down to the anterior sheath) was made in the abdominal wall. The incision, so made, opened to give a 1 cm gap All wounds were smeared with an equal amount of a resistant strain of *Bacillus proteus* and *Klebsiella pneumoniae* to produce conditions similar to those of an abscess

From the second day, the wounds were treated daily with phenytoin or saline and assessed every seventh day using the same parameters (except for pain) used in the clinical trial. Bacteriological examination (swab culture) of all wounds was performed every second day.

Histological examinations were also carried out. On the seven day a biopsy was performed from the upper end of the wound; on the 14th day, from the lower end, and, on the 21st day, from the middle of the wound, whether healed or not After fixation, embedding and sectioning, the tissue was stained with haematoxylin and eosin, van Gieson's and reticulin silver stains. Fifty high power fields were examined independently in all sections by two pathologists who were unaware of the treatment used.

The following histological parameters were assessed· (1) inflammation and infection as assessed by the presence of inflammatory cell infiltration (polymorphs, monocytes, eosinophils), vascularization, fragmentation of collagen (tissue oedema), necrosis and bacteria, (2) healing as assessed by the presence of healthy granulation tissue, fibroblast proliferation, collagenization, and epithelialization. Each parameter was assessed on a scale ranging from −, not present to + + +, marked.

Statistical comparison of the data from the phenytoin and control groups was performed using Student's t test or the non-parametric Wilcoxon rank sum test as appropriate

Results

Clinical

After drainage, and at the initiation of phenytoin or control treatment, all abscess cavities contained large amounts of markedly adherent slough and inflammatory exudate with varying degrees of inflammation and induration. In the phenytoin treatment groups, separation of the slough, along with the appearance of healthy granulation tissue, occurred in 48–72 h in all patients. Reduction of inflammatory exudate and of the oedema of the wound base and margin gave the wound a healthy appearance in 19 patients. Within this period, the patients complained less and less of local pain.

In comparison, in the control group, separation of the slough did not begin until at least 5 days after initiation of treatment. In 11 patients, separation did not occur until day 10. Healthy granulation tissue began to appear at days 10–15 but, even so, substantial slough persisted in 11 patients. Both inflammatory exudate and wound base and margin oedema also persisted in 19 patients, giving the wound an unhealthy appearance for up to 15 days in nine patients. Pain continued to be a prominent feature of these wounds. Differences in the appearance of the control wounds and those treated with phenytoin were still observable at 30 days.

Mean percentage reductions in size of wound and mean rates of wound area and volume reductions are summarized in *Table 1*.

A subset of eight matched cases were selected from the group treated with phenytoin and the control group on the basis of equal wound area or volume at the initiation of therapy When wound area reduction in the two groups was compared at day 10 and day 20, the difference was significant (Student's paired t test; $P<0·001$ and $P<0·025$, respectively). When wound volume reduction in the two groups was compared over the period of 10 and 20 days, the difference was also significant (Student's t test; $P<0·005$).

Comparison of the progress of healing of the abscess cavities in both the phenytoin and control groups is shown in *Table 2*. By day 10, 16 of the patients treated with phenytoin had between 50 and 80 per cent healing of their cavities, compared with only four in the control group. By day 20, 17 of those patients treated with phenytoin were almost completely (90–100 per cent) healed. Only one patient in the control group had the same rating.

The only adverse effect of phenytoin application noted was a transient burning sensation

Experimental

In the guinea-pig model, the mean wound contraction rates and percentage area of wound healed at days 7, 14 and 21 are presented in *Table 3*. By day 7, 80·9(10·8) per cent of the initial wound area had healed in animals treated with phenytoin while in controls only 41·3(15·9) per cent of the area had healed. Of the eight animals treated with phenytoin, four had healed completely by day 14 and all eight had healed by day 21, whereas only one of the controls had healed by this time (*Table 3*).

Bacterial cultures were taken every second day from day 2 to day 10. The inoculated *B. proteus* and *K pneumoniae* strains disappeared by the fourth-day culture in the phenytoin group, whereas in controls, at the same time, the number of colonies increased by 4·2 times. The number of colonies decreased with the appearance of healthy granulation tissue from the fifth day onward in both groups. Both the phenytoin and control groups, however, did show contamination by *Staphylococcus aureus* (coagulase +) with significant colony counts.

Table 1 *Percentage reduction in wound area and volume, and mean rates of wound reduction with time in response to treatment (phenytoin versus control)*

	Day 10		Day 20		Day 30	
	Control	Phenytoin	Control	Phenytoin	Control	Phenytoin
Percentage reduction						
Wound area	43·2(11·0)	62·6(7·2)*	66·5(10·5)	94·4(6·4)*	72·2(11·1)	99·7(1·4)*
Wound volume	31·3(5·8)	40·9(8·2)*	66·0(12·1)	86·0(18·1)*	84·7(13·6)	93·5(13·3)
Mean rates of wound reduction						
Wound area (cm^2/day)	1·58(0·51)	2·32(0·48)†	1·19(0·21)	1·80(0·32)†	1·21(0·35)	1·57(0·49)†
Wound volume (cm^3/day)	0·32(0·04)	0·48(0·06)‡	0·34(0·03)	0·50(0·07)‡	0·31(0·03)	0·48(0·02)‡

Values given are mean(s d). * $P<0·01$ (Wilcoxon rank sum tests), † $P<0·05$; ‡ $P<0·005$ (Student's t test)

Table 2 *Percentage wound area healing with time (phenytoin* versus *control)*

Area healed (%)	Day 10		Day 20		Day 30	
	Phenytoin	Control	Phenytoin	Control	Phenytoin	Control
11–20	–	–	–	–	–	–
21–30	–	2	–	–	–	–
31–40	–	8	–	1	–	–
41–50	2	6	–	–	–	–
51–60	6	2	–	1	–	–
61–70	8	2	–	14	–	9
71–80	4	–	1	3	–	6
81–80	–	–	2	–	1	4
91–100	–	–	17	1	19	1

Values represent number of patients

Table 3 *Response to phenytoin-sodium and control treatment (i.e. decrease in wound size) in guinea-pig model*

Animal no.	Day 7		Day 14		Day 21	
	Phenytoin	Control	Phenytoin	Control	Phenytoin	Control
1	2·6	2·2	3·2	3·0	3·5	3·5
2	3·2	0·8	3·5	2·4	3·5	3·2
3	3·2	1·8	3·5	2·3	3·5	3·1
4	2·2	1·0	3·0	2·7	3·5	3·2
5	2·5	1·9	3·0	2·6	3·5	3·1
6	3·0	2·3	3·5	2·4	3·5	2·9
7	2·6	0·9	2·9	2·2	3·5	2·6
8	3·2	1·2	3·5	2·6	3·5	3·0
Average healing	2·80(0·38)*	1·51(0·58)	3·26(0·26)*	2·51(0·26)	3·50†	3·06(0·25)
Average wound contraction rate	0·40(0·05)	0·21(0·08)*	0·47(0·03)	0·39(0·03)*	0·26(0·12)	0·17(0·0)†
Average healing (%)	80·9(10·8)	41·3(15·9)	93·2(7·6)	71·5(8·5)	100·0	87·8(7·5)

Values are mean(s.d.). Difference between phenytoin and control significant at *P* values. $^*P<0·005$; $^\dagger P<0·05$ (Student's *t* test)

Histological studies confirmed the differences between the groups. Biopsies of the control wounds taken at weekly intervals showed marked inflammatory and vascular changes, which decreased gradually with time. Necrosis was still seen in this group, even in the second and third weeks. Partly circumscribed areas of young fibroblastic proliferation, collagenization and prominent vascularity were visible.

Histological examination of biopsies from the group treated with phenytoin showed markedly diminished inflammatory changes, with mild to moderate infiltration of polymorphonuclear cells. In contrast with controls, less necrosis was seen. Earlier appearance of young fibroblasts, mononuclear cells, and eosinophils, as well as collagenization, was a prominent feature with phenytoin. The characteristics of the vascular pattern were also different, with accelerated neovascularization in small patches, evident in the phenytoin group. These observations were confirmed by van Gieson's and reticulin silver stains. No effect of phenytoin on epithelialization was observed.

Discussion

Our studies of the healing of clinical and experimental abscess cavities indicate that the topical application of phenytoin significantly enhances healing when compared with conventional treatment. The fact that the same degree of reduction of wound area was achieved in the group treated with phenytoin at day 10 as in the control group at day 20 is noteable. By day 20, 17 patients treated with phenytoin had healed completely, while only one patient treated conventionally had healed. Our findings are consistent with those of other investigators who have examined the effects of phenytoin on a variety of wounds[4–17], but this is the first clinical and laboratory study of the effects of phenytoin in abscess cavities.

Our observations indicate that characteristics of the effects of phenytoin on healing include reduction of oedema and inflammation, both at the base and at the wound margins, early separation of slough, increased fibroblast proliferation and collagen production, and acceleration of the growth of healthy granulation tissue. We do not know the mechanism by which phenytoin decreases local oedema. It is possible that the effect is due to an anti-inflammatory action[4,11,12,18]. The ability to stabilize the cell membrane and to reduce calcium-dependent release of various cellular products (including lysozymes and collagenase[19,20], insulin[21], calcitonin[22] and neurotransmitters[23–25]) may also contribute to the healing properties of phenytoin. Inhibition of vasopressin release could also be involved[26–28], but with topical application of phenytoin this seems far less likely than a local action.

The reduction of bacterial colonization and infection observed in the group treated with phenytoin could be because of a direct or indirect effect of phenytoin. Additional experience in our clinic on the local use of phenytoin in nine infected hernioplasty cases involving Prolene® mesh (Ethicon, Edinburgh, UK) implants supports the view that phenytoin has anti-inflammatory and, possibly, antibacterial activity. Despite the continued presence of the implants, complete healing was achieved in all patients. Our own unpublished laboratory work suggests that phenytoin may have a direct antibacterial effect. However, local pH changes, improved local circulation and/or immune function in the wounds treated with phenytoin could provide the explanation. Further *in vivo* and *in vitro* evaluation will be necessary to resolve the question

The reported enhancement of fibroblast proliferation[29–31], and collagen production and maturation[30,32–36] by phenytoin may also be important in its wound healing effects. The inhibition of collagenase release[20,37] and thereby collagen breakdown[30,34,37–40] by phenytoin seems likely to play a role. The net result is enhanced granulation tissue formation, collagen content and maturation, and wound contraction.

Our observations, in contrast with those of Shapiro[4], suggest that phenytoin has only an indirect effect on epithelialization. We feel that the increased epithelialization seen with phenytoin is because of its ability to decrease inflammation, reduce oedema and enhance contraction of the wound. Because of these effects, the total period available for epithelialization was 5–10 days greater in the group treated with phenytoin than in the control group.

In future studies, several issues need to be addressed These include the further evaluation of the basic mechanisms of the actions of phenytoin, including its effects on inflammation, bacterial colonization and growth, cell proliferation, and local growth factor production. Dose–response studies are also required. Our observations are based on application of 20 mg/cm^2 with a maximum total topical dose of 300 mg of phenytoin-sodium per daily dressing. This dose was sufficient to accelerate and promote wound healing both in patients and in animals, but we cannot say that it is optimal. Finally, phenytoin absorption studies would be valuable, although indications are that absorption is minimal[13,17]. The only adverse effect we noted was a brief initial burning sensation when the phenytoin-sodium powder was applied. Use of phenytoin in the free acid form (i.e. not the sodium salt) eliminates this problem.

In conclusion, we recommend topical application of phenytoin to promote the healing of abscess cavities. Phenytoin is not only effective, but is safe, easy to use and inexpensive.

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Protein status and metabolic expenditure determine the response to intravenous nutrition – a new classification of surgical malnutrition

To determine whether nutritional and metabolic factors affect the response to intravenous nutrition (IVN) 146 surgical patients were classified according to their protein and metabolic status using direct measurements of body protein and metabolic expenditure. The patients were grouped into four categories: category I, moderate to severe protein depletion without raised metabolic expenditure; category II, moderate to severe protein depletion with raised metabolic expenditure; category III, mild protein depletion without raised metabolic expenditure; and category IV, mild protein depletion with raised metabolic expenditure. After 2 weeks of IVN patients in category I gained a mean(s.e.m.) of 0·43(0·06) kg of body protein ($P<0.001$) *and had significant rises in both plasma transferrin and prealbumin* ($P<0.05$)*; patients in category II gained 0·30(0·11) kg of protein* ($P<0.005$) *and also had significant rises in transferrin and prealbumin* ($P<0.05$)*. Patients in category III lost 0·24(0·11) kg protein* ($P<0.05$) *and had no changes in either transferrin or prealbumin and patients in category IV lost 0 51(0·13) kg of body protein* ($P<0.001$) *and although there was a significant rise in plasma prealbumin there was no significant change in plasma transferrin. When postoperative patients were examined separately, they did not differ significantly from preoperative patients except in category I, where their protein gain was only 0·19(0·10) kg, an amount not significantly different from that gained by patients in category II. In each of the four categories described, the changes in total body protein occurring with 2 weeks of IVN were determined by the relative effects of two competing processes; protein depletion and raised metabolic expenditure. With moderate to severe protein depletion (approximately 30 per cent depletion of body protein stores) there was a marked tendency to gain protein with IVN. When the patient had a raised metabolic expenditure or was postoperative this tendency of depleted patients to gain protein was still present but it was less. With only mild protein depletion (approximately 10 per cent depletion) increases in metabolic expenditure made it difficult, if not impossible, to prevent continuing protein loss in spite of aggressive nutritional support. The patient categories we have described determine the response to IVN and form the basis of a new clinical classification of surgical malnutrition.*

G. L. Hill, G. B. Witney,
P. M. Christie and
J. M. Church

University Department of Surgery,
Auckland Hospital, Auckland,
New Zealand
Correspondence to:
Professor G L Hill, University
Department of Surgery, Fifth Floor,
Auckland Hospital, Auckland,
New Zealand

Surgical patients can be affected by nutritional and metabolic processes. Semistarvation in patients with anorexia, vomiting or partial obstruction results in gradual loss of protein and fat with lowered metabolic rate Compensatory mechanisms are designed to conserve protein and energy[1]. Sepsis or other types of metabolic stress result in rapid breakdown of protein with raised metabolic rate. Compensatory mechanisms are designed to provide essential protein and energy components for healing and repair[2]. From the combination of protein depletion and raised metabolic rate, four categories of malnourished surgical patients may be described; moderate–severe protein depletion, with and without raised metabolic rate, and mild protein depletion, with and without raised metabolic rate. Although isotopic infusion studies suggest[3,4] that protein depletion and raised metabolic rate may influence the responsiveness of surgical patients to nutritional repletion the effectiveness of these four categories in predicting the likely response to intravenous nutrition (IVN) has not been established.

Using objective measurements of protein depletion and metabolic expenditure a large number of surgical patients who required IVN were placed into these categories of surgical malnutrition and their response to a 2-week course of IVN was assessed in terms of changes in body stores of protein.

Patients and methods

Between June 1984 and July 1988, 382 surgical patients with gastrointestinal disease received a course of parenteral feeding on the

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wards of the University Department of Surgery at Auckland Hospital. Of this group 146 completed an uninterrupted 14-day course of IVN and had measurements of body composition and energy expenditure before commencement of feeding and after 14 days. The study was approved by the Auckland Hospital Ethical Committee (July 1983).

After assessment patients were classified into two categories depending on whether they had moderate to severe body depletion or mild protein depletion. These categories were subdivided according to the results of measurement of resting energy expenditure (RME) into four categories:

I Moderate–severe protein depletion, RME not raised
II Moderate–severe protein depletion, RME raised
III Mild protein depletion, RME not raised
IV Mild protein depletion, RME raised.

Clinical data

A clinical profile of each patient was recorded, including age, sex, height, weight, weight loss (percentage of recalled well weight), diagnosis and relationship of the study to surgery. A patient was termed postoperative if the initial assessment was made 5 days or less after a major abdominal operation. In no patient did major surgery occur during the study period.

Assessment of body composition

Body composition analysis was based on a five compartment model of the human body[5,6]. Total body protein (TBP) was calculated from direct measurement of total body nitrogen made by *in vivo* neutron activation analysis[7].

The precision of the estimate of TBP was measured by repeated scanning of an anthropomorphic phantom containing physiological concentrations of the major body elements. This was ±0·30 kg (±2·6 per cent of TBP in Reference Man[8]). An analysis of two human cadavers gave excellent agreement in the measurement of body nitrogen between chemical and neutron activation analysis, to within 40 g (2·7 per cent) in one and 4 g (0·6 per cent) in the other[9].

Total body water was measured by tritium dilution with a precision of 0·6 kg (±1·5 per cent of water of Reference Man)[5,10].

Total body fat was estimated as the difference between body-weight and the sum of total body water, protein, minerals and glycogen. The precision of the estimate is ±0·8 kg (±6·4 per cent of fat in Reference Man), and is most affected by the measurement of total body water. In the analyses of the cadavers, the different estimates, relative to chemical measurements of fat, were high by 0·23 kg in the first and low by 0·94 kg in the second[9].

Assessment of protein depletion

In this study we have classified the intensity of wasting or depletion as mild or moderate to severe[11]. To assess the intensity of protein depletion the measured values of TBP were compared with values predicted from multivariate predictor equations that relate measured TBP to age, height, sex and weight. TBP was measured in 136 normal subjects and was regressed for each sex against the variables age in years (A), height in cm (H) and weight in kg (M) yielding the following regression equations[6]:

Males $\text{TBP (kg)} = 0{\cdot}061\,H + 0{\cdot}126\,M - 0{\cdot}032\,A - 6{\cdot}334$
Females $\text{TBP (kg)} = 0{\cdot}095\,H + 0{\cdot}067\,M - 0{\cdot}018\,A - 10{\cdot}631$

The mean(s.d.) ratio of the measured TBP to the predicted TBP for the normal volunteers was 0·99(0·11) for females and 1·03(0·12) for males, and so patients with a ratio $<0{\cdot}76$ (or 2 s.d. below the mean of the normal population) were considered to have moderate to severe protein depletion.

Assessment of metabolic stress

Indirect calorimetry was used to measure RME. This was performed using a modification of the ventilated hood technique originally described by Kappagoda and Linden[12,13]. The initial measurement was performed under basal conditions in a quiet darkened room after an overnight fast, before any nutritional support had started.

The measured values of RME were compared with values predicted from equations that relate resting metabolic expenditure to the fat free body mass (FFM; the sum of water, protein, minerals and glycogen, in kg). From the normal population the following regression equation was obtained.

$$\text{RME (kcal 24 h}^{-1}) = 13{\cdot}58\ \text{FFM} + 554 \text{ (males and females)}$$

The mean(s.d.) ratio of the measured RME for the normals was 1·00(0·09) and so patients with a ratio $>1{\cdot}18$ were considered to have a raised RME.

Plasma proteins

Plasma albumin, transferrin and prealbumin levels were determined from venous blood drawn immediately before and after the 14-day study period. Plasma transferrin and prealbumin were measured by laser nephelometry using appropriate antisera (transferrin, Behringwerke AG, Marburg, France; prealbumin, Dako, Copenhagen, Denmark). Plasma albumin was assayed on an SMA autoanalyser (Bayer AG, Paris, France) by the bromocresol green method. Normal ranges for our laboratory are 35–50 g l^{-1} for albumin, 200–400 mg 100 ml^{-1} for transferrin, and 17–37 mg 100 ml^{-1} for prealbumin.

Experimental protocol

Immediately after the RME had been determined body-weight and height were measured. After removing 20 ml blood for plasma protein measurements, each patient received 3·7 MBq (100 μCi) tritiated water intravenously, and was then scanned in the *in vivo* neutron activation facility for 36 min. Venous blood, 10 ml, was taken 2·5 h after the ^3H_2O injection; to estimate total body water, the tritium contents of the serum removed from the blood samples were assayed by liquid scintillation counting.

Intravenous nutrition

All patients were fed exclusively by the parenteral route for the duration of the 14-day study period. The nutrient solution contained synthetic amino acids (Synthamin 10 per cent, Baxter Healthcare, New Zealand) and calories as 50:50 dextrose Intralipid® (Baxter Healthcare) mixture. The prescription was for total energy intake of 40 $\text{kcal kg}^{-1}\,\text{day}^{-1}$ with a calorie nitrogen ratio of 150:1. Electrolytes, minerals, trace metals and vitamins were added to the nutrient solution as appropriate and the solutions were made up in 3 litre bags for infusion through a volumetric infusion pump into a central venous cannula.

Data analysis

Unless otherwise stated all data are presented as mean(s.e.m.). The significance of group differences before and after the period of IVN were tested using Student's paired *t* test. Differences between groups were tested by a one way analysis of variance.

Results

Categories

The four categories into which the 146 patients were classified are shown in *Table 1* with clinical data, disease categories and relationships to surgery.

Patients with active Crohn's disease (defined as a Crohn's disease activity index >150[14]) and patients with severe ulcerative colitis (defined according to the criteria of Truelove and Witts[15]) were all confined to categories II and IV. There were no patients with clinically advanced metastatic cancer and none with undrained collections of pus in any of the groups.

Protein status and RME at the beginning of the study

In *Table 2* details of protein status and metabolic expenditure are shown for each of the four categories at the commencement of the 14-day study period. As expected categories I and II had substantial (approximately 30 per cent) deficits of body protein and categories II and IV had a 30–40 per cent increase in RME. Mean plasma protein levels were below our normal ranges for each group although analysis of variance showed no significant differences between the groups for any of the plasma proteins.

Amount of IVN received

All patients had an uninterrupted 14-day course of IVN.
Category I received mean(s.d.) 2188(199) kcal and 13·6(1·3) gN per day;
Category II received 2604(224) kcal and 16·9(1·4) gN per day;
Category III received 2382(72) kcal and 15·7(0·5) gN per day; and
Category IV received 2750(202) kcal and 16·4(1·0) gN per day.

Table 1 *Classification into four categories according to protein and metabolic status*

	Category I ($n=60$) Moderate to severe protein depletion Normal RME	Category II ($n=30$) Moderate to severe protein depletion Raised RME	Category III ($n=33$) Mild protein depletion Normal RME	Category IV ($n=23$) Mild protein depletion Raised RME
Clinical data				
Sex	31M, 29F	18M, 12F	19M, 14F	13M, 10F
Age (years)	54·7(2·5)	48·5(3·2)	57·2(3·6)	51·1(4·1)
Weight (kg)	52·2(1·6)	62·3(2·9)	58·0(2·3)	66·5(2·4)
Weight loss (%)	17·3(1·3)	14·2(1·8)	8·1(1·3)	5·3(1·4)
Diagnosis				
Upper gastrointestinal cancer	12	6	4	3
Lower gastrointestinal cancer	6	–	4	–
Inflammatory bowel disease	17	7	10	5
Enterocutaneous fistula	13	8	8	8
Pancreatitis	3	2	1	1
Other	9	7	6	6
Relationship to surgery				
Preoperation	42	18	19	13
Postoperation	18	12	14	10

Clinical data values are expressed as mean(s.e.m.)

Table 2 *Protein nutrition and resting metabolic expenditure of the four categories at the commencement of the 14-day study period*

	Category I ($n=60$) Moderate to severe protein depletion Normal RME	Category II ($n=30$) Moderate to severe protein depletion Raised RME	Category III ($n=33$) Mild protein depletion Normal RME	Category IV ($n=23$) Mild protein depletion Raised RME
Total body protein (kg)				
Measured	6·31(0·31)	7·77(0·42)	8·67(0·40)	9·18(0·50)
Predicted	9·46(0·34)	10·95(0·52)	9·41(0·5)	10·32(0·50)
Deficit (%)	33·3	29·0	7·9	11·0
Plasma proteins				
Albumin (g/l)	33·2(0·6)	33·2(1·1)	35·3(0·9)	34·6(1·1)
Transferrin (mg dl^{-1})	176(6)	182(14)	200(12)	186(11)
Prealbumin (mg dl^{-1})	15·7(1·0)	16·4(1·9)	16·4(1·4)	16·4(1·6)
Resting metabolic expenditure (kcal kg^{-1} day^{-1})				
Measured	1140(25)	1619(46)	1261(34)	1570(45)
Predicted	1118(20)	1171(24)	1197(25)	1210(27)
Increase (%)	2·0	38·2	5·4	30·0

Values are expressed as mean(s.e.m.)

Table 3 *Changes in body composition over the 14-day study period*

	Category I ($n=60$) Moderate to severe protein depletion Normal RME	Category II ($n=30$) Moderate to severe protein depletion Raised RME	Category III ($n=33$) Mild protein depletion Normal RME	Category IV ($n=23$) Mild protein depletion Raised RME	ANOVA F	 *P*
Weight (kg)						
Day 0	52·2(1·6)	62·3(2·9)	58·0(2·3)	66·5(2·4)	8·102	0·01
Change	−0·03(0·29)	0·69(0·74)	0·31(0·56)	−0·10(0·70)	0·438	n.s.
P	n.s.	n.s.	n.s.	n.s.		
Water (kg)						
Day 0	31·4(1·1)	33·9(1·3)	35·2(1·4)	35·3(1·5)	2·385	n.s.
Change	−0·03(0·18)	−0·23(0·32)	0·45(0·35)	−0·13(0·42)	0·109	n.s.
P	n.s.	n.s.	n.s.	n.s.		
Protein (kg)						
Day 0	6·31(0·31)	7·77(0·42)	8·67(0·41)	9·18(0·46)	12·327	<0·01
Change	0·43(0·06)	0·30(0·11)	−0·24(0·11)	−0·51(0·13)	8·178	0·01
P	0·001	0·005	0·05	0·001		
Fat (kg)						
Day 0	10·68(0·79)	16·97(2·08)	10·86(1·2)	18·17(1·67)	8·737	<0·01
Change	0·14(0·14)	0·63(0·53)	0·91(0·30)	0·55(0·51)	0·573	n.s.
P	n.s.	n.s.	0·005	n.s.		

Values are expressed as mean(s.e.m.), n.s., not significant

Response to IVN over 14-day study period

In *Table 3* the response to the 14-day course of IVN can be seen. In none of the categories was there a loss of total body fat over the study period, suggesting that in categories I, II and IV energy intake was adequate. For patients in category III there was a gain in total body fat indicating an overall positive energy balance for the 14-day study period. The most striking changes in body composition occurred in TBP stores. Categories I and II gained TBP over the 14-day study period although the average gain was less in category II where RME was raised. Where moderate to severe protein depletion was not present (categories III and IV) losses of TBP occurred.

In both categories with moderate to severe protein depletion there were significant rises ($P<0{\cdot}05$) in transferrin (category I 43(10) mg dl^{-1}; category II 60(17) mg dl^{-1}) and prealbumin (category I 7·7(1·4) mg dl^{-1}; category II 10·9(2·8) mg dl^{-1}). In the categories with mild protein depletion only prealbumin in category IV rose significantly (6·8(2·1) mg dl^{-1}). There were no significant changes in plasma albumin for any of the categories.

Differences between preoperative and postoperative patients

When the patients within each category were divided into preoperative and postoperative subgroups the average changes in TBP were not significantly different except in category I. The 42 preoperative patients in category I gained a mean(s.d.) of 0·53(0·14) kg protein over the 14-day study period which was nearly three times the mean amount gained by the 18 postoperative patients in category I (0·19(0·10) kg; $P<0{\cdot}05$). This response to IVN in patients in postoperative category I was not significantly different from that in category II (0·19(0·10) kg for category I compared with 0·30(0·11) kg in category II, n.s.).

Effect of cancer

When the patients within each category were divided into those with and without cancer the mean changes were not significantly different within any of the groups.

Discussion

The results show that the changes in TBP that occurred with IVN were determined by the relative effects of two competing processes, protein depletion and raised metabolic expenditure. The patients with moderate to severe protein depletion significantly increased their protein stores with IVN. When the RME was raised or when the patients were postoperative this natural tendency of the depleted patients to gain protein was still present but less. When mild protein depletion was present even small rises in RME made it difficult if not impossible to prevent continuing protein loss in spite of aggressive nutritional support.

It has long been recognized that the efficiency of protein retention at a given level of protein and energy is increased by prior protein depletion[16]. The mechanism for this is not completely understood. The labile protein pool perhaps remains depleted as long as the body's protein stores are depleted providing a potential mechanism for this increased protein avidity[17]. Investigators using isotopic methodologies, however, have shown how raised metabolic expenditure and other forms of metabolic stress increase whole body protein catabolism to a degree which results in net protein loss in spite of adequate amounts of IVN[4,18]. The present study shows though that moderate to severe protein depletion is able, to some extent, to overcome this effect at least in the type of patients studied here. In situations of major metabolic stress we have measured much larger protein losses. In patients with undrained collections of pus[19] and those on intensive care with serious postoperative sepsis and organ failure[20] we have found losses of approximately 0·1 kg body protein each day whether the patients were initially protein depleted or not and in spite of high intakes of protein and energy.

In this study patients have been placed in categories according to strict definitions and using sophisticated methodology. Before this can be considered an advance in patient care it has to be established that patients can be categorized just as well using simple clinical criteria; a preliminary study suggested that this may prove possible[21]. Applying such criteria to the present population has been less convincing. For instance, if the patients are selected on the basis of a weight loss of greater than 15 per cent only those with this amount of weight loss or more in whom RME was not raised gained TBP. In the other three categories the changes in TBP did not reach statistical significance. Perhaps this is not surprising in view of the limitations of investigating weight loss in isolation from a thorough physical examination[22]. As a consequence a major clinical study is in progress in which a standard protocol for the clinical assessment of protein status and metabolic stress is to be used Early results suggest that the broad categories described will be able to be recognized clinically.

IVN has a beneficial effect in some patients even though body protein stores are not increased[23,24]. Recent work has shown that there is a close association between reserves of body protein and physiological function[25]. Our work has more precisely defined the categories of patients most likely to gain protein with IVN and this may form the basis of a new and practical classification of surgical malnutrition.

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Postoperative hypophosphataemia and muscle function

P. T. Andersen*, E. Toft†, A. K. Hansen‡ and T. Sinkjaer§

**Department of Anaesthesia, Odense University Hospital, Departments of †Clinical Chemistry and ‡Abdominal Surgery, Aalborg Hospital, and §Department of Medical Informatics and Image Analysis, Aalborg University, Aalborg, Denmark*

Correspondence to:
Dr P T Andersen, Department of Anaesthesia, Odense University Hospital, DK-5000 Odense, Denmark

Muscle function tests of the triceps brachii muscle were performed before operation and on the third postoperative day in ten patients undergoing elective cholecystectomy. Electromyograms (EMGs) were recorded by surface electrodes during sustained isotonic and isometric muscle contraction with a constant force of 20 per cent of the preoperative maximal voluntary contraction. Root-mean-square of the EMG was calculated together with the neuromuscular efficiency and measures of the fatiguability. These parameters were compared with changes in the simultaneously measured serum phosphate concentrations. Mean(s.e.m.) neuromuscular efficiency measured after 32–40 s of muscle contraction decreased 14(5) per cent after operation ($P<0{\cdot}01$)*, whereas the mean fatiguability of the muscle was unchanged. Mean serum phosphate concentration was 0·87(0·06) mmol/l before operation and 0·79(0·06) mmol/l 3 days after the operation* ($P>0{\cdot}05$)*. Two patients developed severe postoperative hypophosphataemia (serum phosphate concentration <0·50 mmol/l). Postoperative muscle function deterioration was not associated with changes in the serum phosphate level* ($P>0{\cdot}10$; $r=0{\cdot}03$)*. We conclude that patients undergoing cholecystectomy develop postoperative deterioration in skeletal muscle function, which is not associated with serum phosphate concentration.*

Hypophosphataemia occurs after trauma and after operation[1,2]. Forty-eight hours after elective abdominal aortic bypass surgery a serum phosphate concentration below 0·50 mmol/l (reference range 0·80–1·50 mmol/l) was described in five out of ten patients[3] and within 24 h of hospitalization after head injury five of 19 patients developed hypophosphataemia (<1 mg/100 ml, 0·33 mmol/l) (reference range: 2·50–4·60 mg/100 ml or 0·83–1·52 mmol/l)[4]. The postoperative serum phosphate concentration may further decrease during glucose infusion[5]. The clinical significance of early postoperative hypophosphataemia is uncertain.

Low serum phosphate concentrations in phosphate depleted individuals have been associated with severe reduction of diaphragmatic contractility[6,7]. Elevation of the serum concentration of the intramyocellular enzyme creatine phosphokinase has been found at serum phosphate levels below 0·50–0·65 mmol/l[8]. This suggests that acute functional and/or structural damage to the skeletal muscle cell membrane may be caused by hypophosphataemia[9]. Myopathy occurs in patients with chronic hypophosphataemia[10,11] and recent studies of collapsed, previously healthy exercising adults without prior phosphate depletion have suggested that acute hypophosphataemia may induce acute muscle dysfunction[12,13].

This study attempts to identify a possible association between early postoperative hypophosphataemia and electromyographic estimates of changes in skeletal muscle function and to determine if early postoperative hypophosphataemia is of clinical importance with respect to muscle performance.

Patients and methods

Ten patients scheduled for elective cholecystectomy were investigated. The protocol was approved by the local ethical committee and all patients gave their informed consent before participating The number, age and sex of the patients are given in *Table 1*. All patients underwent elective surgery during general anaesthesia with thiopental sodium, suxamethonium chloride, fentanyl, halothane, nitrous oxide and oxygen During the study no patient received blood transfusion, intravenous diuretics or parenteral nutrition All infusions given were free of phosphate.

Measurement of muscle function and electromyograms The patient was sitting upright in bed during measurement of muscle function. The right arm was fixed at the elbow to a plate The elbow and the forearm rested on the plate with an elbow angle of 90°. The shoulder joint was slightly flexed and abducted and the forearm was semipronated with the thumb pointing directly upwards. The plate was adjusted to end just proximal to the wrist and was connected to a lever system mounted on an axis. The axis of rotation was aligned with the axis of rotation of the elbow joint. In connection with the system a strain gauge measured the torque around the elbow joint Surface electrodes (Medicotest®, Copenhagen, Denmark) were positioned over the lateral head of the triceps brachii muscle for recording of electromyograms (EMGs). The distance between electrode centres was 2 cm and the electrodes were arranged parallel to the muscle fibres. The EMG was amplified (DISA® model 2708, Copenhagen, Denmark) and filtered (20 Hz to 2 kHz) This signal was recorded, together with the torque around the elbow joint, by an FM type tape-recorder (Brüel and Kjaer, Copenhagen, Denmark) for later analysis The placement of the electrodes was marked on the skin to ensure identical electrode positioning before and after operation.

Blood samples were taken from an antecubital vein before operation at about 09.00 hours (non-fasting) and after operation at about 08.00 hours (overnight fast). Serum phosphate concentrations were measured with a Technicon SMA II 12/90 autoanalyser® (Technicon, Tarrytown, New York, USA) The serum phosphate reference range was 0 80–1·50 mmol/l, with an interassay variation coefficient for the phosphate measurements of 2 9 per cent

Experimental protocol The experiments were performed on the day before surgery and on the third postoperative day.

Maximal voluntary contraction (MVC) was measured before operation. The subject maintained 20 per cent of MVC until the muscle contraction felt unpleasant. The muscle function test was stopped before the patient was completely exhausted A 20 per cent contraction level was chosen to obtain a fast development of fatigue in the muscle without inducing pain from the abdominal wound. The effect of the muscle contraction (i.e. the torque) was continuously shown on an oscilloscope

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Table 1 *Clinical data of the patients with sex, age, and preoperative and postoperative serum phosphate concentrations*

Patient no.	Sex	Age (years)	Serum phosphate (mmol/l)	
			Preoperative	Postoperative
1	F	27	0·79	0·69
2	F	52	0·98	0·96
3	F	39	0·72	0·34
4	F	58	1·37	1·05
5	F	36	0·74	0·43
6	M	62	0·62	0·77
7	F	50	1·30	0·75
8	M	61	0·72	0·82
9	F	42	0·87	0·98
10	F	68	1·03	0·94

together with the requested torque level (20 per cent of MVC) giving the patient a visual feed-back of the actual muscle contraction level. After operation the MVC was not measured as this manoeuvre could induce an undesirable tension increase in the abdominal wound, but otherwise the preoperative muscle function measurement procedure was followed.

Data analysis EMGs were fed to an EMG analysing program in an electromyography system (Nicolet®, model Viking, Madison, Wisconsin, USA) In the present study the root-mean-square (RMS) mode for measuring integrated EMG was chosen RMS was measured during an 8 s interval every 30 s elapsed, starting with the interval 2–10 s (zero s indicates the start of the muscle function test). RMS values measured in the 32–40 s interval were stable and fatigue was negligible at this point. Changes in the pre- and postoperative muscle force production were estimated by comparing the pre- and postoperative RMS values from this time interval. The RMS signal was used to monitor the neuromuscular efficiency (NE), which may be calculated when the force delivered by the muscle is known (NE = force divided by RMS). In this experiment the force delivered by the muscle was constant during all muscle function measurements Postoperative NE values were divided by preoperative NE values (NE ratio) calculated in identical time intervals to detect changes in the rate with which NE decreased with time. Changes in the NE ratio reflect changes in the rate of fatigue development in the muscle Torque measurements were not included in our data analysis, but served as a control of the muscle contraction level for each patient.

Statistical analysis Changes in parameters were evaluated by Student's t test For correlational analysis parametric statistics were used A significance level of 0·05 (two tailed) was chosen

Results

Mean(s.e.m.) serum phosphate concentration changed from 0·87(0·06) mmol/l before operation to 0·79(0·06) mmol/l after operation ($0{\cdot}10 > P > 0{\cdot}05$). Two patients had severe postoperative hypophosphataemia (serum phosphate <0·50 mmol/l). Serum phosphate concentrations of these patients were respectively 0·72 and 0·74 mmol/l before operation, and 0·34 and 0·43 mmol/l after operation. The pre- and postoperative serum phosphate concentrations for all patients are given in *Table 1*. Two parameters reflecting muscle function were studied: NE and fatiguability (the reduction of NE with time during the muscle function measurement).

Figure 1 shows the changes in the pre- and postoperative mean NE values with time in the whole patient group. Mean NE decreased with time ($0{\cdot}01 < P < 0{\cdot}05$) before and after operation and mean NE was lower in all time intervals after the operation compared with preoperative values.

Figure 2 shows mean values of the ratio between postoperative and preoperative NE values (NE ratio). The solid line indicates a value = 1. The NE ratio did not change with time ($P > 0{\cdot}10$), indicating that there were no changes in the rate with which the muscle was fatigued before and after operation.

Mean NE measured in the 32–40 s time interval was 14(5) per cent lower 3 days after the operation than before operation ($P < 0{\cdot}01$).

Muscle function measurements lasted for 431(42) s before operation and 360(44) s after operation ($0{\cdot}20 > P > 0{\cdot}15$).

Changes in the serum phosphate concentration were not related to the changes in NE in the 32–40 s time interval ($P > 0{\cdot}1$, $r = 0{\cdot}03$).

Discussion

Previous similar investigations have documented postoperative deterioration in skeletal muscle function and increased fatiguability, but have not managed to identify its cause. The results and conclusions have often been influenced by factors other than the postoperative muscle function (motivation of the patient, pain, etc.)[14,15]. In one study[16] the serum phosphate concentration was compared with the subjective feeling of fatigue on postoperative days 10, 20, and 30, but no association was found.

Christensen *et al.*[17] introduced needle EMG measurements in a later study of postoperative fatigue At sustained contraction of biceps brachii at a force adjusted to 30 per cent of maximum force they found a more pronounced increase in the mean amplitude of the electromyography signal 20 days after operation. On postoperative day 10 they registered no

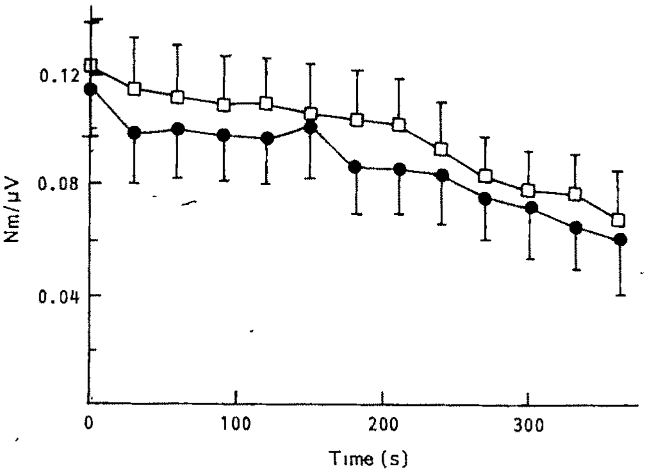

Figure 1 *Preoperative and postoperative (third postoperative day) neuromuscular efficiency (mean(s.e.m.)) of the whole patient group during the muscle function measurements* □, *Preoperative* ●, *postoperative*

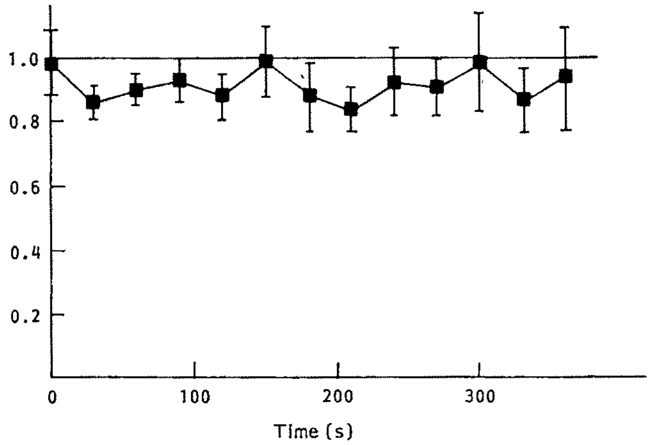

Figure 2 *Neuromuscular efficiency on the third postoperative day divided by preoperative neuromuscular efficiency (neuromuscular efficiency ratio) Mean(s.e.m.) values are given for the whole course of the muscle function measurements*

changes in the EMGs with respect to number of potential reversals exceeding 100 μV/s (turns) or to the mean amplitude between turns During sustained muscle contraction, however, there was an earlier increase of mean amplitude in the postoperative than in the preoperative tests.

The study of postoperative neuromuscular function has been greatly facilitated by the use of EMGs recorded by surface electrodes. The rectified, integrated electromyography signal may be used to monitor neuromuscular efficiency, when the force delivered by the muscle is known (NE = force divided by rectified integrated EMG). NE is a quantification of the excitation–contraction coupling[18] During sustained muscle contraction, several metabolic changes occur: high energy phosphates are reduced, lactate accumulates, pH decreases, and K^+/Na^+ gradients across muscle membranes are altered[19,20]. The combined effect of these changes is a reduction of the force-generating capacity of the neuromuscular system, contributing to the development of fatigue. As a consequence a fall in NE is registered. In the present study NE was reduced by 14 per cent after operation, indicating that the force production of the muscles was reduced. This may contribute to a prolonged recovery period after surgery. The rate of decrease in NE during a sustained muscle contraction may be taken as an indicator of the fatiguability of the muscle group[18]. The ratio between the preoperative and postoperative decrease in NE was constant in our study.

The specific aim of this study was to identify a possible correlation between postoperative hypophosphataemia and skeletal muscle function in patients who were not phosphate depleted before operation. Our patients were all physically fit and without signs of malnutrition. None received medical treatment with diuretics or antacids, and none were known alcoholics or diabetics. The finding of subnormal serum phosphate levels before operation in five patients was surprising on this background These patients may have been phosphate deficient before operation – a presumption supported by the finding of two cases of severe postoperative hypophosphataemia in the patients who were hypophosphataemic before operation *versus* none in the patients who were normophosphataemic before operation.

We conclude that patients undergoing cholecystectomy develop postoperative deterioration in skeletal muscle function, which is not associated with the serum concentration of phosphate

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Importance of the omentum in the development of intra-abdominal metastases

R. J. Lawrance, M. Loizidou, A. J. Cooper, P. Alexander* and I. Taylor

*Departments of Surgery and *Medical Oncology, Southampton General Hospital, Southampton SO2 6RE, UK*

Correspondence to:
Mr R. J. Lawrance

Areas of trauma are preferred sites for metastatic tumour growth. In extensive intra-abdominal tumour recurrence the omentum is invariably involved. The importance of the omentum in the development of tumours at sites of intra-abdominal trauma has been investigated. Colonic anastomoses were performed in Hooded-Lister rats with and without omentectomy. Animals received intraluminal or intraperitoneal injections of a syngeneic tumour. With intraluminal injection, tumour occurred at the anastomosis and in the omentum in 38 and 43 per cent of animals respectively but following omentectomy the values were 14 and 9 per cent (omental remnant). With intraperitoneal administration tumour occurred in 53 per cent at the anastomosis and in 79 per cent in the omentum compared with 16 and 29 per cent (in omental remnant) following omentectomy. In this model a reduced ability of an anastomosis to support 'seeded' tumour following removal of the omentum is demonstrated and the development of local recurrence from spilled tumour cells during operation may be enhanced by, or be dependent on, the proximity of the omentum.

Local recurrence of colorectal cancer occurs commonly[1,2] due to incomplete excision of the primary tumour[3] or development of a new tumour in an area of unstable epithelium around the site of the original tumour[4]. Viable tumour cells are shed both intraluminally and intraperitoneally at the time of resection and local recurrence may be due to direct seeding at, or around, the colonic anastomosis[5,6]. Implicit in such an hypothesis is the assumption that the wound is a preferred site for growth of shed tumour cells. This would appear to be the case for blood-borne cancer cells which, in an experimental animal model, are 10000 times more likely to grow at the site of a colonic anastomosis than within the intact colon[7].

The object of this study was to determine whether tumour growth occurs preferentially at the site of a colonic anastomosis or whether growth is determined by spread from adjacent tissues into the anastomosis.

Following intraperitoneal injection of carcinoma or sarcoma cells the growth of solid tumours occurs most readily on the omentum[8]. The importance of the omentum in influencing local recurrence around a healing anastomosis could be a clinically important factor and this aspect was investigated in this study.

Materials and methods

Animals and tumour

Syngeneic Hooded-Lister rats (male and female, matched weight 150–200 g) maintained as an inbred line were used.

All experimental procedures were performed under ether anaesthesia.

The tumour used was a syngeneic, methylcholanthrene-induced fibrosarcoma, MC28. This particular tumour has similar behavioural characteristics to adenocarcinomas when used in experiments involving tumour seeding at specific sites[7,9]. It has the advantage that a single cell suspension of high viability can be regularly produced.

Preparation of tumour cell suspensions

Using mechanical and enzymatic disaggregation, as previously described[9], a single cell suspension of MC28 tumour in Hank's Balanced Salt Solution (HBSS) was obtained. Cell counts and viability were determined by trypan blue dye exclusion, and the concentration of viable tumour cells was adjusted by dilution of the parent suspension to give 5×10^2, 1×10^3, 1×10^4, 5×10^4, 1×10^5, and 1×10^6 viable cells per ml.

Omentectomy

The stomach, spleen and greater omental leaf were delivered via an upper midline incision. Omentectomy involved removing as much of the omental tissue as possible from the hilum of the spleen (conserving the splenic artery), from the greater curve of the stomach (removing the epiploic arcade) and from the retrogastric extension of the omental leaf. Haemostasis was by the clip-crush method. No animal died as a result of this procedure. After a period of 3–4 weeks the animals underwent the experimental methods described.

Intraperitoneal and intraluminal tumour cell injections

The descending colon was delivered via a low midline incision and a colonic anastomosis fashioned using 6/0 interrupted silk sutures.

Tumour was administered intraperitoneally as a tumour cell suspension in 1 ml of HBSS before final closure of the muscular layer of the abdomen. If no laparotomy was performed (group a, *Table 1*),

Table 1 *Determination of the threshold tumour dose for intraperitoneal or intraluminal tumour*

	No. of animals developing intra-abdominal tumour			
	Intraperitoneal injection		Intraluminal injection	
No. of MC28 cells injected	a	b	c	d
1×10^5	3/3	3/3	4/4	–
5×10^4	–	–	4/4	0/5
1×10^4	4/4	3/3	3/5	0/5
5×10^3	4/4	4/4	–	–
1×10^3	2/5	3/5	0/5	–
5×10^2	0/5	1/5	–	–

Growth of MC28 at sites within the abdomen. Group a, no laparotomy, group b, laparotomy and colonic anastomosis; group c, laparotomy and colonic anastomosis; and group d, laparotomy but no anastomosis. Tumour grew on the omentum, on wounds or both

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then the suspension was administered through a 25 Fr needle inserted in the midline

Tumour was administered intraluminally via a 25 Fr needle injection in the transverse colon, 2–3 cm proximal to the anastomosis in a volume of 0·2 ml HBSS. The volume of the injectate and the distance from the suture line were such to cause minimal distension and thus disruption around the anastomosis Cetrimide was then applied to the injection site and the laparotomy wound was closed using continuous 2/0 silk sutures.

Post-mortem examination

Animals were killed at 18 days after cell inoculation when it was possible to discern foci of tumour within the abdomen and thus the point of tumour take Tumour was recorded as being present or absent at several sites: the omentum (in the control group), the omental remnant, i.e tissue remaining in the lesser omentum and splenic hilum (in the omentectomy group), the laparotomy wound; the colonic anastomosis; the parietal peritoneal surface, the gonadal fat pads; and other sites including the mesentery, diaphragm, etc.

Statistical analysis

The variations in tumour take observed in each group were analysed using χ^2 cross tabulation with Yates' correction.

Determination of the threshold tumour dose (TD_{50})

The aim of this experiment was to determine the tumour dose required to yield a positive tumour take in 50 per cent of animals inoculated. Four groups of rats were used and subdivided into subgroups receiving different doses of tumour cells (*Table 1*) under the following conditions

Group a	Intraperitoneal tumour percutaneously
Group b	Intraperitoneal tumour following laparotomy and colonic anastomosis formation
Group c	Intraluminal tumour following laparotomy and colonic anastomosis formation
Group d	Intraluminal tumour following laparotomy only

Determination of the role of the omentum on the development of intra-abdominal tumour

To determine whether tumour growth around a colonic anastomosis following intraperitoneal or intraluminal introduction of syngeneic tumour cells required initial seeding on the omentum, the incidence and pattern of tumours were compared in rats with intact omenta (controls) and rats following omentectomy

Control group (n=64). All animals underwent laparotomy and colonic anastomoses as described above. Animals were then divided into two groups and tumour was seeded either intraluminally ($n=36$) or intraperitoneally ($n=28$) in cell inocula corresponding to the TD_{50} for each group, i.e. 1×10^4 cells in 0·2 ml HBSS and 1×10^3 cells in 1·0 ml HBSS respectively.

Omentectomy group (n=66). Following omentectomy (see above) each animal underwent a laparotomy and colonic anastomosis, and the same tumour inoculum was given as for the controls with $n=31$ for intraperitoneal and $n=35$ for intraluminal injections.

The animals were allowed to recover and the site and mass of tumour was assessed at post mortem as described.

Results

Incidence of intra-abdominal tumours following inoculation

Table 1 shows the incidence of intra-abdominal tumours following the inoculation of different numbers of tumour cells by either the intraperitoneal or intraluminal route. When given intraperitoneally, intra-abdominal tumour growth occurred equally readily in rats that had undergone a colonic anastomosis and in those that had not (total 13 of 21 *versus* 14 of 20). Tumour growth following intraluminal injection, however, was only seen in rats that had undergone a colonic anastomosis (11 of 18 *versus* 0 of 10). Following intraluminal injection, therefore, tumour cells leak into the peritoneum via the anastomotic suture line and not via the needle track. Based on these findings, tumour growth in rats with an intact omentum were compared with those which had undergone an omentectomy following injection of 1×10^3 cells intraperitoneally or 1×10^4 cells intraluminally.

Tumour growth following omentectomy (Table 2)

The incidence of intra-abdominal tumours following both intraperitoneal and intraluminal inoculation of tumour cells was significantly lower in rats that had undergone omentectomy compared to those with an intact omentum, (19 of 66 *versus* 37 of 63, $\chi^2=8{\cdot}3$, d.f.$=1$, $P<0{\cdot}005$).

In both groups of rats, intra-abdominal growth of tumour was, to a large extent, associated with growth on the omentum or omental remnant.

In the control groups, tumour growth at the colonic suture line only occurred when growth involved the omentum. In some of the animals, growth involved the omentum in the absence of growth on the anastomosis (7 of 15, intraperitoneally; 2 of 15 intraluminally).

In the omentectomy groups, tumour grew on the anastomosis in a greater proportion of animals when the omental remnant was involved (3 of 9 intraperitoneally; 2 of 3 intraluminally), compared with when it was not (2 of 22, intraperitoneally; 3 of 33, intraluminally).

Discussion

In this model a significant reduction in the 'take' of tumour at sites of trauma (i.e. anastomotic and laparotomy wounds) was demonstrated following intraperitoneal or intraluminal inoculation when maximal amounts of omental tissue were removed. The omentum may act as an initial site for tumour 'take' and 'secondary seeding' occurs at sites of trauma. The

Table 2 *Effect of omentectomy on tumour growth after injection of 1×10^3 cells intraperitoneally or 1×10^4 cells intraluminally*

	Specific sites of tumour development (no. of animals)				
Animal groups	Anastomosis	Wound	Gonadal fat	Peritoneum	Mesentery
Controls					
Intraperitonally ($n=28$)					
Tumour on omentum (22/28)	15	13	14	9	7
None on omentum (6/28)	0	0	0	0	0
Intraluminally ($n=35$)					
Tumour on omentum (15/35)	13	13	14	13	7
None on omentum (20/35)	0	0	0	0	0
Omentectomy					
Intraperitonally ($n=31$)					
Tumour on omental remnant (9/31)	3	4	5	1	5
None on omental remnant (22/31)	2	3	5	0	1
Intraluminally ($n=35$)					
Tumour on omental remnant (3/35)	2	1	2	2	1
None on omental remnant (32/35)	3	0	2	1	2

observation that anastomotic tumour is always perianastomotic and does not proliferate intraluminally and that the omentum (in the control groups) is invariably adherent to the site of trauma lends support to this suggestion.

Several mechanisms may be involved in the ability of the omentum to support tumour growth:

1. The omentum has the innate ability to 'gather' particles passively from the peritoneal cavity be they carbon particles, starch granules, bacteria or tumour cells[10] Adhesion to the omental surface by tumour cells occurs, in general, by attachment to microvilli and pseudopodia on the mesothelial cell surface[11]. Alteration in the morphology of the mesothelial cell allows access by the tumour cell through the basement membrane. Adhesion and invasion may be facilitated around the areas of lymphoid aggregates (milk spots) where discontinuity between the mesothelial cells overlying them allows exposure of underlying protein molecules[12]. That particles become adherent to localized areas may allow for a concentration of viable tumour cells to occur around areas of lymphoid activity (namely macrophages), whereupon the survival of a cluster of cells into a viable metastasis is greatly enhanced[13,14].

2. Macrophage activity around the milk spots could lead to the secretion of polypeptide growth factors which may enhance tumour growth since stimulation of omental macrophages results in increased tumour on the omentum[15].

3. The subsequent development of the micrometastases on the omentum into overt metastases depends on the neovascularization of the lesions[16]. Secretion of angiogenesis factors by omental tissue may result in early vascularization of seeded tumour and, therefore, more rapid growth[17].

In practical terms what does this model offer? In principle, the use of TD_{50} doses of tumour cells rather than inocula in excess of the TD_{100} used by other workers[18,19] leads to a more sensitive experimental model. Removing the bulk of the organ mainly responsible for the development of intra-abdominal tumour renders the peritoneal cavity more refractory It may be possible to study the relative importance of other sites within the abdomen in tumour development hitherto masked by the effects of the omentum and to study factors which could influence survival of cells seeded intraperitoneally with greater accuracy.

It is known that ovarian micrometastases are found in the omentum early in the disease and omentectomy is necessary for accurate disease staging[20]. Gastrointestinal tumours, particularly in the stomach, metastasize directly to omental lymph nodes via lymphatics and transperitoneal spread of any tumour invariably involves the omentum[21] The effect of the human omentum on the ability to support growth of single cell suspensions of tumour by mechanisms outlined above remains unclear. The omental properties of adhesion to inflamed areas, angiogenesis and ability to support epithelial cell growth suggest potential human parallels.

The wisdom of carefully enveloping a colonic anastmosis with omentum following curative resection for cancer in order to reduce the risks associated with leakage[22] may be challenged. Adequate lavage should be undertaken to destroy viable desquamated tumour cells in the peritoneal cavity and in the gut lumen.

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Paper accepted 5 June 1990

Correspondence

Aetiology of venous ulcers

Letter 1

Sir
We read with interest the paper by Stacey *et al.* (*Br J Surg* 1990, 77 1050–4) in which the authors study the effect of various treatment regimens on transcutaneous oxygen pressure in patients with healed venous ulcers. We would dispute, however, their statement that ‘reduced oxygen tension lends support to the theory that skin hypoxia may be an important factor in venous ulceration’ Their own data seems to refute this, as reulceration was not associated with a lower transcutaneous partial pressure of oxygen (P_{tc,O_2}) compared with ulcers that remained healed. To say that this is due to thin skin over the ulcer seems to be an attempt to have one's cake and eat it!

P_{tc,O_2} measurements are made by inducing ‘arterialization’ of the skin capillaries This is done by heating the skin to 43°C to produce maximum vasodilatation To draw conclusions about skin oxygen levels from P_{tc,O_2} readings, therefore, is to assume that the capacity of the skin microcirculation to vasodilate in response to heat is normal. Rayman *et al.* have shown conclusively that this capacity is, in fact, abnormal in one group of patients prone to skin ulceration, namely diabetics[1] We have examined the relationship between P_{tc,O_2} and heat-induced vasodilatation in patients with lipodermatosclerosis (LDS) using laser Doppler flowmetry (unpublished observations). The results showed that vasodilatory capacity in response to heat was markedly reduced in LDS patients compared with normal controls, and that the vasodilatory capacity exhibited a firm correlation with the P_{tc,O_2} This implies that low P_{tc,O_2} levels in venous disease reflect an inability of the microcirculation to increase its flow in response to local heating. The cause of this perfusion defect has yet to be determined. P_{tc,O_2} can be used as a marker of the severity of skin damage in venous disease, but inferences about the oxygen content of liposclerotic skin at normal temperatures cannot be drawn using this technique Having disputed the authors' first statement, we are inclined to agree with their later statement that ‘factors other than skin hypoxia appear to play a significant role in causing recurrent ulceration’.

T. R. Cheatle
S. K. Shami
S. Sarin

Department of Surgery
The Middlesex Hospital
London W1N 8AA
UK

1. Rayman G, Williams SA, Spencer PD, Smaje LH, Wise PH, Tooke JE Impaired microvascular hyperaemic response to minor skin trauma in type 1 diabetes *Br Med J* 1986; **292**: 1295–8

Author' reply

Sir
Mr Cheatle *et al* have misinterpreted the statement regarding skin hypoxia and venous ulceration The transcutaneous oxygen ratios measured over both the healed venous ulcer and over the standard site 7·5 cm above the medial malleolus are significantly lower than those which we have previously measured over normal legs[1]. Clearly this difference from normal implies that skin hypoxia may be an important factor in venous ulceration The transcutaneous oxygen measurements from the standard site were not significantly different in limbs that re-ulcerated compared with limbs that remained healed. The measurements from over the healed ulcer were significantly higher in limbs that re-ulcerated; however, they were still lower than those from normal legs.

The data from our study clearly show, as stated, that the level of the transcutaneous oxygen ratio, although abnormally low, has a poor predictive value for re-ulceration in the individual patient. Their statement that the ‘P_{tc,O_2} can be used as a marker for the severity of skin damage in venous disease’ would, therefore, seem not to be the case except when comparing skin at the site of a healed ulcer with that from a site that has not previously ulcerated

Drawing firm conclusions on skin oxygenation from transcutaneous oxygen readings (measured at 45°C, and not at 43°C as quoted) is indeed unsound and no such ‘firm’ conclusions were drawn in this paper. Their studies using the laser Doppler are interesting and are one aspect that we are also currently investigating at Fremantle Hospital They have a simplistic concept of the microcirculation of the skin if they consider the laser Doppler to measure only ‘vasodilatory capacity’ when the skin is heated

M. C. Stacey

University Department of Surgery
Fremantle Hospital
Fremantle
Western Australia, 6160

1. Stacey MC, Burnand KG, Pattison M, Lea Thomas M, Layer GT. Changes in the apparently normal limb in unilateral venous ulceration. *Br J Surg* 1987, **74**: 936–9

Letter 2

Sir
In your September issue you published two well argued letters from Dr Michel and Messrs Coleridge-Smith and Scurr commenting on Mr Burnand's leader on venous ulceration (*Br J Surg* 1990, 77. 1071–2) In the same issue, Stacey *et al.* from Mr Burnand's group published a paper on the effect of treatment on transcutaneous oxygen tension in patients with healed venous ulcers. The methodology reported in this latter paper helps explain why our understanding of the aetiology of venous ulcers is so poor.

No matter which hypothesis we subscribe to (and I fear that I also have doubts about the fibrin cuff hypothesis) there is almost universal agreement that, in patients with venous ulcers, elevation will lead to healing We also know that once compression is removed, if a leg with a healing venous ulcer and healthy granulation tissue is allowed to remain dependent, the granulation tissue becomes unhealthy and oedematous within a frighteningly short time. We know to advise our patients against standing still or sitting with their feet at floor level It is hardly surprising that we remain confused about the aetiology of venous ulcers when many of the physiological measurements relating to tissue oxygenation and perfusion are performed, as Mr Stacey and his colleagues have done, ‘with the patient lying supine’. There would only be a point in measuring tissue oxygenation in patients with elevated legs if the fibrin cuff hypothesis is accepted. Mr Stacey's observation that the P_{tc,O_2} was, if anything, slightly higher in patients who subsequently re-ulcerated must surely have caused some doubt in their minds. especially as re-ulceration at 12 months was most frequent with Stanozalol and elastic stockings and least frequent with elastic stockings alone

C. McCollum

Department of Surgery
University Hospital of South Manchester
Manchester M20 8LR
UK

Influence of glucagon on protein and leucine metabolism

Sir
I read with interest the paper by Pacy *et al* (*Br J Surg* 1990, 77: 791–4) describing the catabolic effects of glucagon in relation to protein loss and muscle protein turnover.

I think it is an error not to have mentioned the work of Wilmore and others[1] who have already described the effects of glucagon along with cortisol and catecholamines, and labelled these the ‘stress hormones’, responsible for many of the metabolic changes seen after injury or during major sepsis.

While it is difficult to quantify the effects of a hormone without studying its metabolic effects in isolation, the omission of the possible role of the other components of the stress response is inaccurate, since these act synergistically and facilitate effects not present when studied separately

Thus, to suggest inhibiting the action of one, i.e. glucagon, is to ignore and misunderstand the whole response. Modification of the stress response to reduce protein breakdown and nitrogen loss will require a more subtle intervention at a cellular level rather than blocking one hormone or adding another.

P. Burgess

Lecturer and Trauma Fellow
Department of Surgery
University of Louisville
Kentucky
USA

1. Bessey PQ, Watters JM, Aoki TT, Wilmore DW. Combined hormonal infusion simulates the metabolic response to injury. *Ann Surg* 1984; **200**: 264–81.

Authors' reply

Sir

We are aware of the pioneering research work of Wilmore and colleagues in Harvard relating to the investigation of the integrated metabolic response to injury[1,2]. However, we studied specifically the influence of glucagon on protein kinetics and felt it more appropriate to focus the quoted references on this hormone. We deliberately did not mention the possible role of other counter-regulating hormones in the absence, to date, of relevant data from our laboratory. We chose to study hormonal action in relative isolation while fully appreciating the constraints that such an approach imposes We felt that single hormone manipulation would both simplify data interpretation and exclude the problem of which range of hormones should be infused to most closely mimic the overall stress response. For example, in the study quoted by Burgess[1] neither growth hormone or noradrenaline were provided. Reports suggesting that counter-regulatory hormones act synergistically in general metabolic control[1–3] provide no unequivocal evidence of such control with particular regard to protein metabolism[4] In part, this may relate to difficulties in achieving comparable hormone levels during single or multiple hormonal administration[1] Certainly the most beneficial means of altering the metabolic response due to an acute inflammatory insult will require a considerably more subtle intervention than merely inhibiting glucagon. Indeed, we are currently investigating this point. However, in the light of our present findings, we believe that reducing glucagon levels after surgery may ameliorate the observed abnormalities in protein metabolism.

P. Pacy
D. Halliday

Clinical Research Centre
Nutrition Research Group
Harrow HA1 3UJ
UK

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Tumour markers in screening

Sir

I read with interest the leading article by Dr Roulston (*Br J Surg* 1990; 77 961–2) concerning the use of tumour markers for screening for malignant disease. In light of the current emphasis on preventative medicine and screening in general practice it is indeed wise to highlight some of the limitations of tumour markers in this regard It is particularly important to remind ourselves that the most useful numerical guide to the value of a screening test is the positive predictive value (rather than the specificity or the sensitivity) and that it is the prevalence of the disease rather than any other factor which has the major influence on this value.

The commonest male cancer is carcinoma of the prostate[1] It is increasing in incidence both due to improved methods of detection and also due to a 'real' increase in the incidence of the disease. The management of prostate cancer has in recent years benefited from the use of the serum marker prostate specific antigen (PSA) The use of PSA to screen for early-stage (and therefore curable) disease is limited by the fact that raised levels are not specific for cancer Benign prostatic hyperplasia is associated with moderately high levels which overlap with those obtained from patients with early prostate cancer Despite this potential drawback we have examined the role of PSA as a screening tool for carcinoma of prostate A population of men between the ages of 55 and 70 in a large city general practice have been screened for prostate cancer with a digital rectal examination and measurement of serum PSA,. From a total of 422 men screened to date, seven cancers have been detected. In each case the serum PSA was elevated above the cut-off point of 4 mg/litre and each cancer is organ-confined and, therefore, potentially curable The positive predictive value of a PSA level greater than 4 mg/ml in detecting cancer is 10 per cent At a cost of £3 per test this represents a cost-effective method of detecting a potentially curable condition which all too often presents at a stage when only palliative treatment can be offered

D. Chadwick

Department of Urology
Southmead Hospital
Bristol BS10 5NB
UK

1. Silverberg E, Lubera JA Cancer statistics 1989. *CA-A Cancer J Clin* 1989, **39**: 3–20

Reducing renal ischaemia during transplantation

Sir

The importance of minimizing the ischaemic damage suffered by transplanted kidneys during implantation has been emphasized by Forsythe *et al*. (*Br J Surg* 1989; **76**: 999–1001). The insulating jacket described by them offers one solution to the problem of rewarming, but the method of insulation used routinely in Oxford, during the past 15 years, is equally effective, simpler, and only requires materials that are readily at hand.

This method employs a surgical glove with knotted fingers, which is partially filled with crushed frozen normal saline, followed by the kidney, and after adding more ice the opening of the glove is tied with thread. The rubber is incised over the hilum, and the vessels allowed to protrude ready for anastomosis. As long as there is ice in the glove the kidney remains cold.

In response to the paper by Forsythe *et al*. we have tested the efficacy of the glove. Six pairs of pigs' kidneys cooled to <1°C were rewarmed under simulated operating theatre conditions; one kidney of each pair was insulated using the glove method, and the other was not insulated. The core temperature of uninsulated kidneys rose to $25{\cdot}2 \pm 3{\cdot}8$°C by 45 min, compared with the insulated kidneys where the temperature rose to $12{\cdot}8 \pm 4{\cdot}3$°C These results were very similar to those reported by Forsythe *et al*, but unfortunately the insulating jacket was unavailable for direct comparison.

In practice, our median (range) anastomosis time is 40 (28–61) min, and we achieve a primary function rate of 72 per cent while employing a simple and adequate method of insulation

J. A. Roake
G. J. Toogood
A. P. Cahill
D. W. R. Gray
P. J. Morris

Nuffield Department of Surgery
University of Oxford
John Radcliffe Hospital
Oxford OX3 9DU
UK

Correspondence

Colorectal liver metastases

Sir

We read with interest the paper by Hunt *et al.* describing the recent clinical trial of regional chemotherapy with 5-fluorouracil (5-FU) and degradable starch microspheres (DSM) in patients with colorectal liver metastases (*Br J Surg* 1990; 77 779–82)

However, there are a number of issues concerning the methodology which may influence interpretation of the results First there must be some doubt whether the patients received the optimum dose of DSM to effect complete hepatic arterial blockade and intrahepatic redistribution of cytotoxic drug. Although the amount of DSM administered was monitored in some patients in their study it is not clear whether this was employed during each treatment session. We feel this is an important omission since we have found that the optimal dose of DSM varies as the hepatic tumour burden progresses or regresses. Consequently administering standard aliquots of DSM may result in either inadequate embolization or back-flow of the starch microspheres to the splanchnic organs together with the co-injected cytotoxic drug Furthermore, as part of the monitoring procedure ^{99m}Tc-macroaggregated albumin particles (MAA) were initially injected before DSM administration to assess regional perfusion[1]. This does not take into account the potential arterial blockade that can be produced by these large MAA spheres (5–40 μm) Examining a similar group of patients with hepatic metastases we have used a scintillation probe linked with a computer (Spherex R monitoring system, Pharmacia, Sweden) to measure the passage through the liver of a radiolabelled low molecular weight marker which has negligible specific uptake or metabolism in the liver. Using this method we have been able to measure the degree of arterial blockade induced by the starch microspheres and thereby accurately determine the optimal dose for individual patients

Two further sub-groups may also have been worth examining in detail Firstly those patients with significant arteriovenous shunting (measured by monitoring the relative increased passage of ^{99m}Tc-human serum albumin microspheres through the liver after DSM administration) would tend to benefit less from this form of treatment since complete arterial blockade with standard sized DSM could not be achieved[2]. This may partly explain the relatively poor results in those patients with >50 per cent hepatic replacement with tumour since this group would tend to have a greater degree of arteriovenous shunting. Second, the other group would be those patients with hypovascular metastases. From our experimental studies it appears that hepatic regional injection of DSM leads to a redistribution of arterial flow from areas of high liver blood flow to low flow areas[3]. Therefore, patients with relatively hypovascular tumours would gain maximum benefit from this therapy.

Finally, the temporary embolizing effect of DSM will only tend to be fully exploited with bolus infusions of drugs. Therefore, 5-FU, which is best administered as a continuous intra-arterial infusion, would appear to be an inappropriate cytotoxic drug to use in conjunction with DSM We have been using bolus doses of mitomycin C (which is cell cycle non-specific and particularly selective towards hypoxic cells) mixed with DSM followed by a continuous infusion of 5-FU at 4-week intervals in an EORTC pilot study Interestingly although there have been several complete and partial objective responses with liver metastases, rather disappointingly, there is progression and eventual death from extrahepatic metastases These observations would suggest that there is perhaps also a role for systemic chemotherapy. Furthermore, we too have found significant technical problems with the Port-A-Cath® (Pharmacia Ltd., Milton Keynes, UK) catheters, particularly occlusion.

We believe that the potential therapeutic benefit of co-administration of DSM with cycotoxic drugs has yet to be realised Possibly with the choice of a more appropriate cytotoxic agent and more precise optimization of the dose of DSM required to achieve arterial embolization, this therapy may yet prove to be useful in the treatment of hepatic metastases

T. G. Cooke
D. Chang*
D. Nott*
S. Jenkins*

Department of Surgery
Royal Infirmary
Glasgow G31 2ER
*and *Royal Liverpool Hospital*
Liverpool L7 8XP
UK

1 Britten AJ, Flowerdew ADS, Hunt TM, Taylor I, Ackery DM, Fleming JS A gamma-camera method to monitor the use of degradable starch microspheres in hepatic arterial chemotherapy *Eur J Nucl Med* 1989; **15** 649–54.
2. Starkhammer H, Hakansson L, Morales O, Svedberg J. Effect of microspheres in intra-arterial chemotherapy A study of arterio-venous shunting and passage of a labelled marker *Med Oncol Tumor Pharmacother* 1987, **4**· 87–96
3. Chang D, Jenkins SA, Nott DM, Grime S, Cooke T Will biodegradable emboli enhance regional chemotherapy for hepatic metastases *Br J Cancer* 1989; **60** 467.

Authors' reply

Sir

We would like to give the following replies to each of the points raised as follows:

1 DSM monitoring was performed regularly on all patients once the procedure was established, but not at every treatment session. Generally it was performed every 2–3 months It should be noted, however, that little change in the required DSM dose was observed in our patients. In our experience 900 mg (the dose given before monitoring was available) was found to be excessive due to arteriovenous shunting and extrahepatic perfusion in these patients.
2 Theoretically it is true that the use of MAA in the monitoring procedure could add to the blockade. However, it is worth noting that our results are compatible with other studies on the effects of DSM with and without MAA.
3 Although the examination of further sub-groups would be of academic interest arteriovenous shunting and tumour vascularity can only be measured by the insertion of a hepatic arterial cannula or other highly invasive investigations. It must be concluded, therefore, that the identification of these sub-groups is clinically irrelevant as treatment would not be withheld after insertion of a hepatic arterial cannula even if less benefit was to be obtained within the specific sub-groups
4. 5-FU or FUDR still remain the most effective single agents for colorectal cancer as opposed to mitomycin C. Continuous infusion is restricted to a certain extent by the expense of the arterial pump systems which are now available
5. We would entirely agree that the progression of extrahepatic disease is extremely disappointing (36 per cent of cases in our study) and that there is a vital role to be played by systemic chemotherapy if an effective form of such treatment can be demonstrated.

I. Taylor
T M. Hunt

University Surgical Unit
Southampton General Hospital
Southampton SO1 6HU
UK

Primary gastric carcinoids

Sir

Davies *et al.*, (*Br J Surg* 1990, 77 1013–14) recommend a conservative approach to the patient with a primary gastric carcinoid The authors recommend endoscopic resection if the tumour is <2 cm in diameter, loal resection if the lesion is >2 cm without muscle invasion and a somewhat nihilistic approach to the patient with a tumour >2 cm with muscle invasion as the prognosis is poor no matter what treatment is offered.

To follow such a treatment policy requires accurate preoperative diagnosis and assessment and I am impressed that all nine of the cases reported were diagnosed at preoprative endoscopy and biopsy. Many of the previously reported cases of primary gastric carcinoids, as with carcinoid tumours elsewhere in the gastrointestinal tract, are in fact only diagnosed after resection[1]. To improve the diagnostic accuracy based on the endoscopic biopsies requires addition of argentaffin and argyrophil stains, along with immunoperoxidase stains where indicated, to the routine haemotoxylin and eosin stains It has been shown that 7 per cent of all gastric malignancies previously diagnosed as adenocarcinomas in fact were carcinoids or mixed tumours[2].

In those tumours >2 cm the proposed treatment is based on the presence or absence of muscle invasion. How was this assessed before treatment? Of the six cases reported with carcinoids >2 cm, three had muscle invasion These were the three treated by gastrectomy. Two of the remaining three patients underwent polypectomy. It is difficult to draw conclusions about the absence of muscle invasion in these cases. Also it is not surprising that the only patients with positive nodes were the three patients who underwent resection, it is not possible to define nodal status in a patient undergoing polypectomy or wedge excision.

The authors do not mention gastric carcinoma arising in patients with pernicious anaemia yet pernicious anaemia patients represent the single largest group of patients predisposed to developing gastric carcinoids[3]. Screening with endoscopy has been advocated and the prevalence of gastric carcinoids in pernicious anaemia patients screened endoscopically has been estimated at 4.1 per cent[4]. In many there are multiple small carcinoid tumours present. There is much to suggest that these gastric carcinoids behave differently than those found in patients without pernicious anaemia[5]. Over 50 patients with gastric carcinoid tumours associated with pernicious anaemia have been reported in the literature and only three have definitely metastasized, two to regional nodes and only one to the liver. This is in contrast to the overall metastatic rate of 55 per cent for gastric carcinoids and hepatic involvement in 24 per cent. When associated with non-antral gastritis without pernicious anaemia the metastatic rate is intermediate[3]. The authors do not comment on whether or not their carcinoids were associated with pernicious anaemia. The five who did well had multiple small carcinoids similar to those in association with pernicious anaemia. The four patients with a single large tumour did badly, with one exception who only had a 15 month follow-up. The single, large gastric carcinoid found in the absence of pernicious anaemia should be considered as a separate clinical entity and treated differently from the multifocal disease often associated with pernicious anaemia.

Whilst suggesting a relatively conservative approach for gastric carcinoids overall it is worth remembering the differences when they are in association with pernicious anaemia and the fact that these tumours are often difficult to diagnose and assess fully before definitive treatment has been undertaken.

R. C. Stuart

North Tees General Hospital
Stockton-on-Tees
Cleveland TS19 8PE
UK

1. Gueller R, Haddad JK. Gastric carcinoids simulating benign polyps. *Gastrointest Endosc* 1975; **21**: 153–5.
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5. Harvey RF, Bradshaw MJ, Davidson CM, Wilkinson SP, Davies PS. Multifocal gastric carcinoid tumours, achlorhydria and hypergastrinaemia. *Lancet* 1985; **i**: 951–4.

War wound excision

Sir

I was interested in the comments in the recent edition made by Mr Coupland (*Br J Surg* 1990; **77**: 833). I note that he comments that the work of Fackler has perhaps adversely influenced the re-writing of the Emergency War Surgery NATO Handbook. It is important to emphasize to your readers that the NATO Handbook referred to is the 2nd United States Revision. The revision has been carried out entirely by authors from the USA, with there having been, to the best of my knowledge, no consultation with their NATO allies. Most of the surgical specialists from the NATO allies would support Mr Coupland's remarks.

I. R. Haywood

Colonel L/RAMC
Joint Professor of Military Surgery
Royal College of Surgeons of England
and Royal Army Medical College
London SW1P 4RJ
UK

Management of gunshot wounds

Sir

In our article (*Br J Surg* 1990; **77**: 652–5) we stated that no immediate complications were incurred from failure to debride the wound track or from retained missiles. Although this held true for all patients in our series, two subsequent patients have developed sepsis in relation to the site of bullet lodgement. On both occasions the missiles were retained within the musculature of the anterior abdominal wall having traversed the peritoneal cavity producing hollow visceral injuries for which laparotomy was undertaken. Neither bullet was palpable at the initial laparotomy and they were, therefore, not removed. Both patients subsequently developed localized abscess formation related to the site of lodgement requiring reoperation and debridement. While this appears to be an uncommon complication, it would suggest that missiles contaminated by intestinal contents should be removed if easily accessible. The comments made by Cooper and Ryan[1] are extremely pertinent in this respect.

D. J. J. Muckart
A. T. O. Abdool-Carrim
B. King

Department of Surgery
University of Natal
PO Box 17039
Congella
Durban 4013
South Africa

Book reviews

Pathways in Medical Ethics

A. G. Johnson 140 × 215 mm Pp 167 Illustrated. 1990 Sevenoaks Edward Arnold. £6 95 softback.

This book is most timely. It is also very appropriate that it should be written by a practising surgeon, someone who perhaps more than any others comes face to face with real ethical issues which demand reaction and solution without delay.

Although, of course, there have been important ethical aspects to the practice of medicine throughout its entire history, ethical matters have come to the fore in recent years as never before Partly this is because completely new issues, e g. those relating to transplantation and *in vitro* fertilization have developed, and partly because of the greatly increased involvement and interest among other professions and the public at large Professor Johnson devotes the first, and larger part of the book called 'Finding the paths', to defining the main ingredients of ethical problems, tracing the history of formative influences and responsibility for making rules and then an analysis of the aims of medical care, the values put on human life, autonomy and consent, and the central issue of truth and integrity. In the second part he gives clear illustrations of pathways of ethical decision making in a series of important current areas of medical practice. The liberal use of algorithms is a prominent feature of giving guidance through the various ethical mazes.

This is not a dry, dusty treatise, but is thought-provoking, stimulating, entertaining, and illustrated by a series of delightful cartoons. Who but a surgeon would have the courage to condense the main tenets of all the world's major religions, plus a few athestic sects, and who but a surgeon could accomplish that in six and a half pages!

Professor Johnson deals in this excellent book with enough controversial matter that he has taken care not to stir up any other unnecessary criticism by ensuring that he uses the female pronoun an almost exactly equal number of times to the male, and this is a rare and refreshing encounter A delightful touch is his inclusion of important extracts of famous international codes on ethical issues within the text of a chapter rather than add them as appendices because, as he claims, 'the appendices of most books are not read!'.

This book will appeal to students of all ages, and is likely to stimulate much further thoughtful discussion.

I. E. Gillespie

Department of Surgery
Manchester Royal Infirmary
Manchester M13 9WL
UK

Handbook of Critical Care

J. L Berk, J. E. Sampliner. 235 × 155 mm. Pp 896. Illustrated 1990 Boston Little Brown. £32.50 softback

This is a multi-author book with many of its chapters written by world authorities. Inevitably, since it is aimed at a wide range of readers, including nursing staff, it does not explore any particular topic in great depth. Nevertheless, most subjects are submitted to a balanced review without heavy emphasis on techniques of unproven value

There is a good deal of discussion of surgical aspects of the critically ill patient This includes a chapter on the surgical treatment of ischaemic heart disease. The problems of nutritional support, sepsis and its treatment are dealt with adequately.

My main criticism is the order of the chapters Multiple organ failure is a major problem in intensive therapy In this book it is discussed in the third chapter, well in advance of more specific topics Similarly, oxygen therapy is discussed after the chapter on controlled ventilation.

This type of idiosyncrasy aside, this is a very good book, well produced, pleasant to handle and easy to read.

J. C. Stoddart

Consultant in Charge
Intensive Therapy Unit
Royal Victoria Infirmary
Newcastle upon Tyne NE1 4LP
UK

Complications of Urologic Surgery. Prevention and Management

Smith and Erlich 190 × 265 mm Pp. 665. Illustrated, 1990 London W B. Saunders. £61.00 hardback

This is a multi-author work which aims to describe the complications of the full range of urological surgery, covering in addition associated medical problems, complications of radiotherapy, etc. The authorship is almost entirely American and the feeling of the lawyer peering over the author's shoulder is inescapable in places. Perhaps the British urologist can no longer ignore this constraint on his practice

While some contributors confine themselves strictly to the causes, prevention and management of complications. others seem to work on the basis that correct operative technique is the best way of avoiding complications, with a varying emphasis on the complications themselves. Thus, this is in many ways a textbook of operative surgery, although one made somewhat uneven by the individual author's different interpretations of their remit There is some repetition; for example, radical retropubic prostatectomy has a chapter to itself, but also is covered in some detail in the chapter on transabdominal prostatectomy, and, in places, illustrations taken from other works do not always accurately match the text.

Reading this book has taught me much that will improve my practice However, I fear that many who would benefit from reading it will find this comprehensive and well produced hardbound book too expensive to buy their own copy, and in the UK at least it probably is destined for the institutional library shelf. This is a pity as the concept of the book is admirable, and a more modest, economically produced paperback work, which individual surgeons could own and regularly consult, would be a real contribution to urological surgical care.

D. Kirk

Western Infirmary
Glasgow G11 6NT
UK

Noninvasive Diagnostic Techniques in Vascular Disease

E F Bernstein 190 × 240 mm Pp 359 Illustrated in colour and black-and-white. 1990 St Louis Mosby-Year Book Inc £60 00 hardback

This volume contains contributions from 42 authors in 33 chapters covering 12 subject areas in the field of non-invasive vascular measurement Rather than reiterating much of what has already been written on this subject in connection with plethysmographic measurement in several previous comprehensive reviews, this volume turns its attention almost exclusively to the new technology embodies in the most recent ultrasound systems and assesses the impact of these on the modern vascular laboratory Chapters from well known and respected experts in their field cover aspects of carotid artery, peripheral vascular and venous examination as well as renal blood flow and mesenteric blood flow assessment The application of the recently introduced technique of colour flow-mapped ultrasound imaging is discussed in detail in connection with these areas providing an up-to-date account of the most advanced aspects of vascular assessment in common usage. In order to illustrate better the results of such examinations several images are reproduced in colour as well as monochrome The only test of the microcirculation to receive attention is transcutaneous oximetry which appears a little out of place in this volume. Finally, two interesting chapters cover what may be possible in the future with still more advanced technology The use of image processing to enhance existing images and achieve three-dimensional reconstruction from ultrasound is considered, followed by a summary of the application of magnetic resonance imaging to blood flow measurement in peripheral vascular disease.

P. D. Coleridge Smith

Middlesex Hospital
London W1N 8AA
UK

Notices and announcements

17–19 February 1991
4th Annual Congress of the North American Society of Phlebology
Florida, USA
Information Connie Simms, Executive Director, North American Society of Phlebology, 204 N. El Camino Real, Suite E234, Encinitas, CA 92024, USA

8–9 March 1991
Surgical Masterclass: Laparoscopic Surgery
Edinburgh, UK
Information Mrs Maureen Webb, Education and Meetings Secretary, Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

1 March 1991
Aneurysmal Surgery
Bristol, UK
Information Mr M. Horrocks, Department of Surgery, Bristol Royal Infirmary, Marlborough Street, Bristol BS2 8HW, UK

14 March 1991
Children and Surgery
Edinburgh, UK
Information NAWCH (Scotland), 15 Smith's Place, Edinburgh EH6 8HT, UK

25–26 March 1991
Injury Research Group Meeting
Newcastle upon Tyne, UK
Information. Dr R N Barton, North Western Injury Research Centre, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK

3–5 April 1991
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Oxford, UK
Information Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

17–19 April 1991
International Conference on Railway Suicide
London, UK
Information Professor R Farmer, Charing Cross and Westminster Medical School, 17 Horseferry Road, London SW1P 2AR, UK

17–20 April 1991
Kocher Symposium: Endocrine Surgery
Berne, Switzerland
Information Mr K. Schluep, Johnson and Johnson AG, Rotzenbuhlstrasse 55, CH-8957 Spreitenbach, Switzerland

18–21 April 1991
SAGES 1991 Scientific Session
California, USA
Information Program Committee, SAGES, Suite 409, 1271 Stoner Avenue, Los Angeles, CA 90025, USA

22–25 April 1991
4th International Symposium on Cardiovascular Pharmacotherapy
Geneva, Switzerland
Information ISCP'91, c/o AKM Congress Service, PO Box CH-4005, Basel, Switzerland

4–5 May 1991
5th International Meeting of the Australian and New Zealand Society of Phlebology
Sydney, Australia
Information: Dr G. Mark Malouf, Secretary, ANZ Society of Phlebology, PO Box 2166, North Parramatta 2151, Sydney, Australia

8–11 May 1991
Melanoma '91, Brighton International Melanoma Conference
Brighton, UK
Information Dr N. Kirkham, Department of Histopathology, Royal Sussex County Hospital, Brighton BN2 5BE, UK

8–11 May 1991
XXVIth Congress of the European Society for Surgical Research and the VIIIth Tripartate Meeting of The Surgical Research Society and The Society of University Surgeons
Salzburg, Austria
Information ESSR Congress Office, 1st Surgical Department, Landeskrankenanstalten, Müllner Hauptstrasse 48, A-5020 Salzburg, Austria

15–18 May 1991
Annual Meeting of the American Association for Cancer Research
Houston, Texas, USA
Information American Association for Cancer Research, Public Ledger Building, Suite 816, Sixth and Chestnut Streets, Philadelphia, PA 19106, USA

17 May 1991
British Association for Endocrine Surgeons
Cambridge, UK
Information Mr A W Goode, Surgical Unit, 4th Floor Alex Wing, The Royal London, London E1 1BB, UK

20–24 May 1991
Pacific Association of Paediatric Surgeons 24th Annual Meeting
Hong Kong
Information Secretariat, PAPS Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

30 May–1 June 1991
4th International Symposium on the Biology, Immunology and Surgery of the Greater Omentum
The Netherlands
Information Secretariat, 4th International Omentum Symposium, Mrs W. J. Buys–Utrecht Cancer Research Centre, Servaasbolwerk 14, 3512 NK Utrecht, The Netherlands

June 1991
33rd Annual Meeting of the International College of Angiology
Singapore
Information International College of Angiology, 1044 Northern Blvd., Ste 103, Roslyn, New York 11576, USA

2–14 June 1991
Methods of Immunologic Research and Diagnosis
Buffalo, New York, USA
Information James F. Mohn, Director, The Ernest Witebsky Center for Immunology, 272 Sherman Hall, Buffalo, New York 14214, USA

6–8 June 1991
5th European Congress of the Society for Surgery of the Shoulder and the Elbow
Wurzburg, FRG
Information Prof Dr med. J Eulert, Orthpadische Universitatsklinik, Konig-Ludwig-Haus, Brettreichstr. 11, 8700 Wursburg, FRG

9–12 June 1991
Fifth International Conference on Malignant Lymphoma
Lugano, Switzerland
Information F Cavalli, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

14–16 July 1991
Techniques in Pulmonary and Oesophageal Surgery
Liverpool, UK
Information Mr R. J Donnell, Cardiothoracic Centre, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB, UK

25–31 August 1991
International Surgical Week
Stockholm, Sweden
Information Scientific Secretariat, 155, Hauptstrasse 63, PO Box 411, CH-4153, Reinach BL1, Switzerland

1–6 September 1991
6th World Congress in Ultrasound
Copenhagen, Denmark
Information Spadville Congress Service, Sommervaj 3, DK-3100 Hornbaek, Denmark

7–10 October 1991
5th Congress of the European Society for Organ Transplantation
Maastricht, The Netherlands
Information 5th ESOT Congress, Conference Agency Limburg, University Hospital Limburg, PO Box 1918, 6201 BX Maastricht, The Netherlands

7–9 November 1991
3rd Combined Meeting of the Nederlandse Vereniging voor Thoraxchirurgie and the Deutsche Gesellschaft für Thorax-, Herz- und Gefässchirurgie
Maastricht, The Netherlands
Information Organizing Secretariat, Conference Agency Limburg, University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

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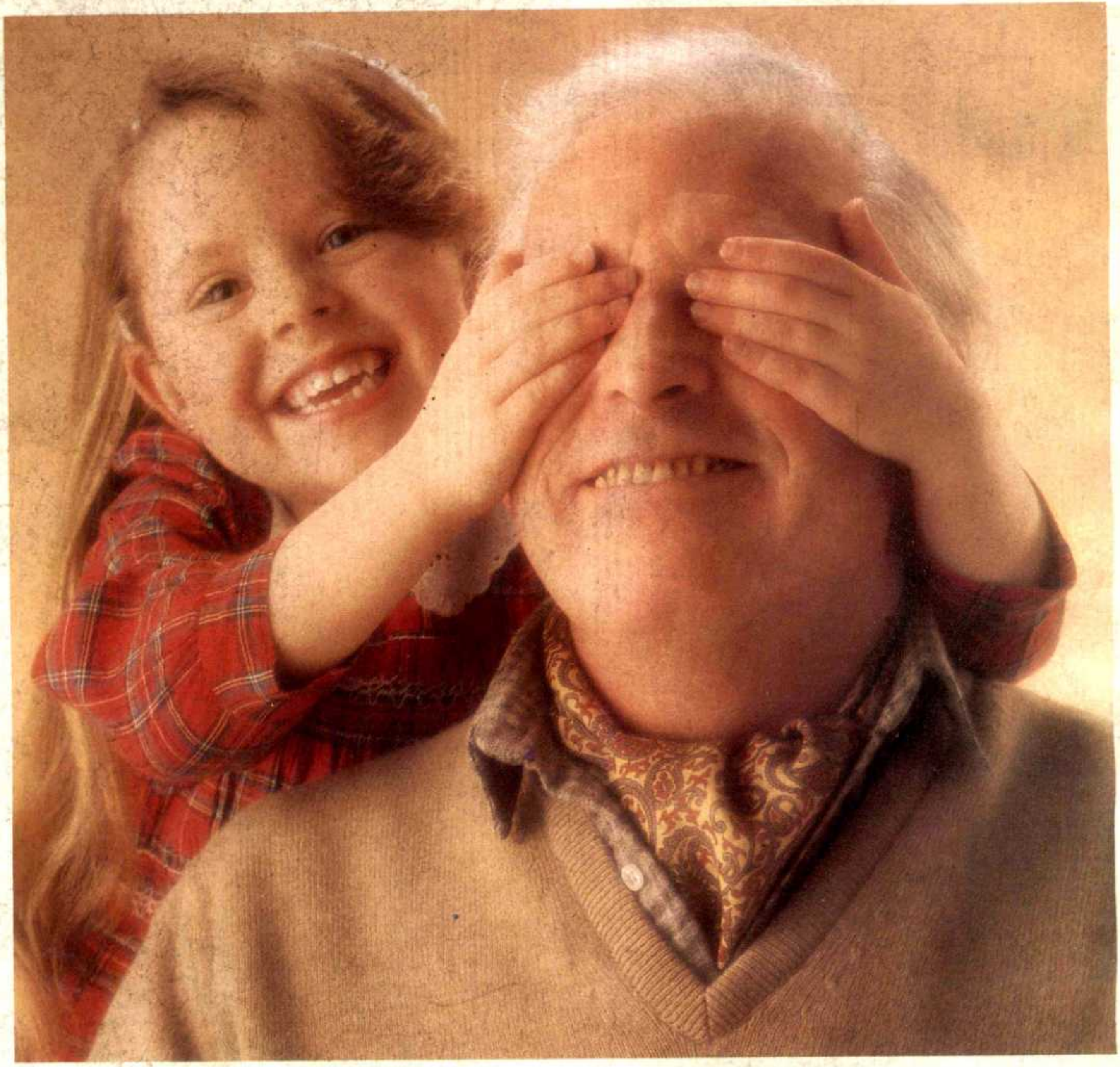

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Reference: 1. Luriglmayr G, Girsch E. In Chisholm G D ed. *'Zoladex' – a new treatment for prostatic cancer. International* Congress *and Symposium Series*. 125. London: RSM Series, 1987: 47-51.

2. Peeling W B. Proceedings of the 'Zoladex' Scientific Launch Meeting 1987.

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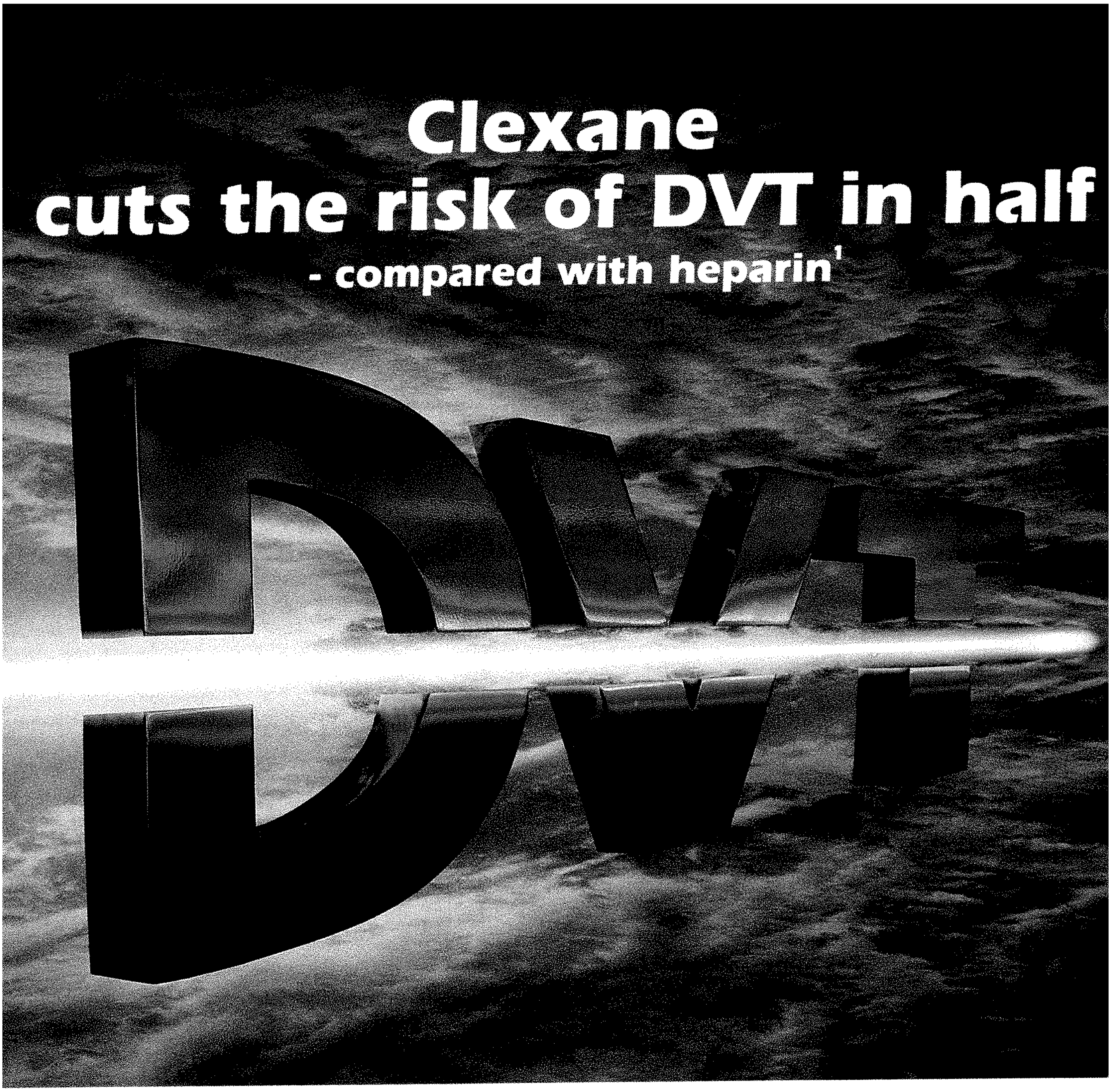

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Cover picture

The Vascular Surgical Society of Great Britain and Ireland

The cover picture shows the chain of office of The Vascular Surgical Society of Great Britain and Ireland.

The President of the society is Mr E J. Williams, FRCS, of St Mary's Hospital, London, UK.

The Secretary of the society is Mr C. V. Ruckley, FRCS(Ed.) Enquiries should be addressed to Mr Ruckley at the Vascular Research Office, University Department of Clinical Surgery. Royal Infirmary, Edinburgh EH3 9YW, UK.

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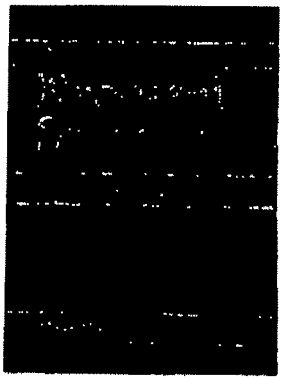

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Resection of hepatocellular carcinoma complicating cirrhosis

Hepatocellular carcinoma (HCC) mainly affects patients with cirrhosis and the presence of cirrhosis appears to be a major prognostic determinant for the following reasons: liver dysfunction and the low capacity to regenerate limit the extent of the resection; increased bleeding tendency and portal hypertension increase the risk of mortality and morbidity; numerous late deaths following resection are related to variceal haemorrhage or liver failure, and the recurrence rate is higher in patients with cirrhosis than in patients without. Therefore, especially in Western countries, experience with surgical resection of HCC in cirrhotic patients has been scanty and disappointing.

Renewed interest in the management of patients with these tumours has been stimulated by the possibility of detecting small tumours with screening and regular follow-up employing sensitive assays of serum α-fetoprotein levels or ultrasonography in high risk patients. An increasing number of reports have demonstrated a reduction in the operative mortality and morbidity of liver surgery in cirrhotic patients[1]. In a forthcoming issue, Paquet and his colleagues[2] confirm that this improvement is the consequence of the increasing number of patients coming to surgery with small HCCs, better patient selection and the extensive use of new techniques in hepatic surgery.

The presence of a small HCC allows limited resection with preservation of as much functional liver parenchyma as possible. Improved understanding of surgical anatomy has permitted liver resection based on the segmental architecture of the liver. Careful patient selection can be achieved with knowledge of the Child's classification, liver biopsy, measurement of nontumour liver volume and measurement of hepatic functional capacity by indocyanine green clearance or galactose elimination. Major technical innovations are available in hepatic resection. Intraoperative ultrasonography is now an indispensable tool in surgery of HCC in cirrhotic patients. This technique provides the most accurate intraoperative method for detecting intrahepatic tumours and facilitating precise resection with a tumour-free margin[3]. Use of an ultrasonic dissector and temporary pedicle inflow occlusion reduces bleeding associated with transection of the parenchyma[4].

Over the last five years, series reporting a large experience of resection of HCC in cirrhotic patients have shown that operative mortality had fallen to less than 10% and that the 3 year survival rate after resection was almost 40%[1,5–7]. One of the most important findings of these studies is that the results of resection were similar in Oriental and Western series. It was previously thought that the high rate of alcoholic cirrhosis in Western countries could result in differences in the structure of the tumour. However, it has since been shown that encapsulation, differentiation and histological grading were not different in Japanese and European patients[5,6]. Therefore, the results of the various treatments reported from Asian countries should be achievable in Western countries.

Survival after resection is affected by two factors; the underlying liver disease and recurrence of the tumour. In a forthcoming issue, Paquet and colleagues will show that preoperative endoscopic procedures can prevent postoperative variceal haemorrhage and should therefore be considered[2]. Poor liver function was predictive of late mortality, and more than half the patients in Child's group B and C died of progression of their liver disease within one year without tumour recurrence[5,6]. This finding clearly raises some doubts about the benefit of resection in patients with poor liver function.

In patients with good liver function, the main factors that have been found to be favourable predictors of survival after resection of HCC are the absence of symptoms, a low preoperative serum α-fetoprotein levels, tumour size less than 5 cm, presence of a tumour capsule, and absence of microsatellite tumours[1,5–7]. As the prognostic factors can only be documented completely after detailed histological examination of the resected specimen, the indications of resection should be broadened in patients with good liver function.

However, the long term results of resection of HCC have been disappointing,

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principally because of the high rate of intrahepatic recurrence. We have already shown that the cumulative recurrence rate reached 100% at 5 years[5]. Long term survival can be observed in a few patients with recurrence, particularly in those treated by a second hepatic resection. Recurrent tumours in our experience were mostly located in the remnant liver and might be due to unrecognized multifocal HCC, inadequate resection of the original tumour or multicentric origin of HCC in cirrhotic patients. Preoperative arteriography with ultrafluid lipiodol injection followed by computed tomography scan 10 to 15 days later is the most sensitive approach for detecting adjacent small tumours and should be performed routinely before resection. The high cumulative intrahepatic recurrence rate observed could well be the consequence of a limited resection. Therefore, the tumour-free margin should be as wide as possible. Nevertheless, several factors are consistent with the view that recurrence after resection might be, at least in some patients, related to new primary tumours in the liver remnant. Those factors are the long interval between resection and recurrence, the location of intrahepatic recurrence distant from the surgical margin in 80% of cases and the difference in α-fetoprotein production after resection.

Resection, alcohol injection, transcatheter arterial embolization and liver transplantation have greatly extended the range of options in the treatment of HCC complicating cirrhosis. In cirrhotic patients with poor liver function where the benefit of resection is not obvious, alcohol injection and transcatheter arterial embolization might be the treatment of choice. In patients with good liver function with a small encapsulated tumour and low α-fetoprotein levels, long term survival can be expected after resection. The high rate of intrahepatic recurrence of HCC after resection suggests that other types of treatment or adjuvant therapy may be needed in these patients. The good prognosis following liver transplantation for cirrhosis with incidental HCC has extended the indications for this procedure in the treatment of HCC complicating cirrhosis. However, the results of liver transplantation have been disappointing in patients with unresectable tumours[8]. In cirrhotic patients with resectable tumours, liver transplantation should be considered but the dilemma faced by the clinician in choosing between resection and liver transplantation is difficult to resolve. If transplantation is chosen, careful patient selection remains crucial because of the limited resource of donors' livers.

J. Belghiti

Service de Çhirurgie Digestive
Hôpital Beaujon
Clichy-Paris
France

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Specialization in general surgery

General surgery is the residue of surgical practice that remains after the separation of the major surgical specialties such as neurosurgery, orthopaedics and cardiothoracic surgery. In many hospitals in the United Kingdom urology is still practised by general surgeons, but there is a continuing process of separation of this specialty as well. The area that is known as general surgery has been shrinking for many years, so it is not surprising that some general surgeons feel threatened by this process of contraction[1].

Within general surgery there is an increasing desire for surgeons to develop and practice in a field of particular interest to them[2]. The three major areas of subspecialization are vascular, gastrointestinal, and breast/endocrine surgery. Most consultant appointments now require that a candidate should offer a special interest, and many specify the field required[3]. This subspecialization offers the opportunity to achieve higher standards of care, and greater job satisfaction for the surgeon.

Around the world the trend towards specialization is at different stages, but is universal. It is perhaps most well developed in the USA, where, for example, a colorectal specialist may call on the help of colleagues in the disciplines of urology, gynaecology and vascular surgery during a difficult pelvic procedure. In Australasia the situation is more akin to that found in the UK. Many surgeons in district hospitals and private practice continue to work in the broad range of general surgery but, particularly in the teaching hospitals, specific areas of interest are increasingly required. In India, where generalism remains the rule, specialists in fields such as vascular surgery are beginning to appear.

A similar process of increasing specialization is occurring in continental Europe. In Germany, although some large units remain very general, capable of performing not only complex gastrointestinal surgery but also vascular and thoracic surgery, others have specialized in one of these areas. Surgical practice in Germany is characterized by the tendency to refer major and complex surgery to specialist centres, rather than to perform these procedures in every district hospital. This concentrates the specialized work in the referral centres. For example, in a recent survey of pancreatic resection which recruited cases from all over Germany, there were three centres which contributed more than half the cases. These centres performed an average of 4, 6 and 9 cases per month (Buchler, personal communication). In France too, specialization is now accepted as the norm. Patients prefer to consult a specialist rather than a generalist, in the belief that the specialist will offer better treatment. Furthermore, established surgeons are happier to accept a new colleague who has a specifically defined area of practice and who will impinge less on their own practice.

The French have also recently formalized the distinction between university surgeons and others. Intending academics must now decide their career choice before medical graduation, so that they can pursue studies leading to a Doctorate of Sciences. Subsquently the young surgeon must proceed to an *internat* in a teaching hospital, during which time he will perform further research for a medical doctorate. There are clearly good arguments to support this emphasis on a research training at an early stage in an academic surgical career, but it is too early to say what will be the effects on recruitment and final performance.

What is to be the future of general surgery in the United Kingdom? 'General surgery' will continue to exist, but I believe that most general surgeons will practice in a major subspecialty, and will restrict their 'general' surgical activity to intermediate cases and the provision of emergency cover. In a survey conducted for the Association of Surgeons in Training[2], the replies from consultant surgeons indicated that future vacancies in their hospital would almost always be filled by a surgeon with a special interest. It is of particular interest that of those consultants surveyed who had not been asked to provide a special interest at the time of their appointment, all but one had subsequently done so. This survey obtained a response from 75 per cent of all general surgical senior registrars in the United Kingdom at that time. All but five intended to practice as consultant general surgeons with a special interest. Three-quarters of them wished to spend at least half of their time in this special area; however, virtually all wish to remain general surgeons rather than subspecialize completely. I have seen nothing to suggest that this desire to specialize has decreased amongst surgical trainees since the survey.

Urology and general surgery are now separate specialties. Surgical senior registrars

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with a training in urology were all more than two years beyond general surgical accreditation and have now been appointed to consultant posts. It is extremely unlikely that there is any surgical senior registrar currently accredited or training for accreditation in both general surgery and urology. This will clearly oblige surgeons who are appointing a replacement for a colleague who practised urology to decide which of these two specialities they require.

General surgeons now have to examine their working practices and training programmes to determine their response to this trend for specialization. In elective surgery this is relatively easy, because it is after all elective surgery which constitutes the basis of the specialization. Within each hospital there should be allocation of the elective work so that it is quite clear which surgeon will be dealing with vascular surgery, major gastrointestinal resections or breast and endocrine surgery.

The consequences of this specialization for the management of emergency cases have not yet been fully thought through. In some districts the vascular surgeon(s) provide emergency cover for vascular cases, perhaps because they are the only surgeons equipped to do so, or perhaps they and their colleagues recognise that a vascular specialist is more likely to obtain good results in these particularly demanding cases. We have not yet applied similar arguments to the management of major gastrointestinal emergencies such as toxic dilatation of the colon or haemorrhage, but it could be argued that if a hospital has one or two gastrointestinal surgical specialists, then they should manage such cases. Major trauma remains a difficult area, because the skills required so often cross specialty boundaries[1]. Interdisciplinary care, though difficult, may be necessary.

How can we train surgeons to meet this need for increasing specialization? Rotations should be better planned and more attention given to the training needs of the senior registrar. The rotations should be designed to give trainees exposure to surgeon(s) who are practising varied specialist interests. Most surgical trainees will have made their specialist choice by the time they become senior registrars. Their training rotation should then be planned to include at least two years work with the appropriate specialists. Training needs must have priority over service requirements if we are to provide the next generation of surgeons with specialist skills. Attempts need to be made to define approximate numbers of trainees for vascular, gastrointestinal and breast/endocrine surgery[2] and those making a career choice should be advised appropriately.

As registrar training programmes become more structured there is a growing tendency for trainees to spend all of their surgical training in one or at most two regions. This may narrow their surgical horizons in comparison with previous generations. In order to provide specialist training which may not be available locally, there must be increased flexibilty towards secondments to other rotations within this country. It should not always be necessary for trainees to go overseas in order to obtain appropriate specialist training. Recent moves in coloproctology to enable secondment on a day release basis suggest that UK surgeons are beginning to recognise this.

In conclusion, general surgery has a future, but this future requires increasing subspecialization. We must aim to provide adequate specialist training, and yet still equip future surgeons with the skills necessary for correct management of emergency cases within 'general surgery'.

C. D. Johnson

University Surgical Unit
Southampton General Hospital
Southampton SO1 6HU
UK

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Thrombolytic therapy in the management of acute limb ischaemia

J. J. Earnshaw

Vascular Studies Unit, Bristol Royal Infirmary, Marlborough Road, Bristol BS2 8HW, UK
Correspondence to:
Mr J. J. Earnshaw

Acute limb ischaemia poses a threat to both the limb and life of a patient. Until recently, attempted revascularization by thrombo-embolectomy or vascular reconstruction held the best chance of limb salvage. Thrombolytic techniques afford an alternative method of management for this condition and are effective in selected patients. Low-dose intra-arterial streptokinase is the most established method of thrombolysis, although the recently developed tissue plasminogen activator offers a promising alternative. Intra-arterial thrombolysis is not an easy option, being labour intensive and requiring close co-operation between surgeon and radiologist. Thrombolytic and surgical techniques are not mutually exclusive but are best used to complement each other. Ideally patients with acute limb ischaemia should be managed by surgeons with knowledge of, and access to, optimal current surgical and non-surgical techniques.

As little as 80 years ago the only treatment for acute limb ischaemia was amputation. The first embolectomy was attempted by Ssabanajeff in 1895, but was unsuccessful[1]. Surgical techniques for blood vessel repair were necessary before arterial surgery could become routine, and it was not until 1911 that limb circulation was first restored by embolectomy[2]. Embolectomy remained an infrequent operation with only 129 cases recorded up until 1933[3]. Many techniques were subsequently devised to aid removal of occluding thrombus including massage, flushing, suction and bougienage[4-6]. The greatest advance was the development of the balloon embolectomy catheter in 1963 by Thomas Fogarty *et al.*[7] which resulted in improvements both in amputation and mortality rates[8]. Excellent results have been achieved, not least in Fogarty's clinic, where 739 patients have been treated with a 95 per cent limb salvage rate in survivors, although additional vascular surgery was frequently required at the same time, or following embolectomy[9].

However, in many reports on acute limb ischaemia the results are less than satisfactory. Some emboli, in particular those distal to the popliteal artery and those with delay in presentation, have inferior results from embolectomy[10,11] A substantial proportion of patients with acute limb ischaemia have *in situ* arterial thrombosis secondary to progression of atherosclerosis[12]. This is an increasing problem as the prevalence of rheumatic heart disease declines and the population ages. Some patients with emboli have associated peripheral arterial disease complicating their management[9].

Distinction between thrombosis and embolism is difficult, but pre-existing claudication suggests the former and a clinically evident embolic source suggests the latter. Balloon extraction may relieve a thrombotic occlusion, but thrombectomy alone is often insufficient to restore the circulation in this situation[13] It is well documented that amputation is more likely following acute thrombosis than after embolism (28 *versus* 13 per cent) although death is more common after embolism (17 *versus* 9 per cent) due to pre-existing cardiac disease[14-17]. Urgent reconstruction is the procedure of choice in acute thrombotic occlusion[17] and recent advances in vascular surgical techniques have improved the range of options available, although it is suggested that graft patency rates may be inferior after urgent reconstruction[18]. A limb salvage rate of 62 per cent and a mortality rate of 19 per cent have been reported using an aggressive surgical approach[19]

However, even recent results for the treatment of acute limb ischaemia have not exceeded 70 per cent limb salvage[14-17,20]. This has led to the suggestion of a 'wait and see' policy with urgent surgery only for acute 'total' ischaemia including a neurological deficit. The remainder are reassessed after a few days of anticoagulation therapy and surgery as required is planned after angiography. This policy offers the stated advantage of a reduced mortality rate, trading 'limbs for lives'[21,22].

An alternative to these surgical and non-surgical approaches is the use of fibrinolytic agents to restore limb circulation. This might offer advantages, particularly in selected high-risk cases.

Development of fibrinolytic therapy

John Hunter was aware of an anticoagulant in the blood of stags chased to their deaths[23], but it was Dastre who coined the term fibrinolysis for the property of clotted blood eventually to redissolve[24] In 1933 when Tillett and Garner noted that streptococci produced a substance, later named streptokinase, capable of lysing thrombi, not only was a therapeutic agent discovered but also a tool with which to investigate the fibrinolytic system[25].

In the 20 years following the discovery of streptokinase, the molecular pathways of fibrinolysis were described Briefly, fibrin is broken down to its degradation products by plasmin, the active form of plasminogen, a circulating plasma protein Plasminogen can be activated by endogenous activators, since termed tissue plasminogen activator (t-PA) and urokinase (discovered by McFarlane and Pilling in urine in 1947[26]), or exogenous activators such as streptokinase (*Figure 1*)

The fibrinolytic system is inhibited at two levels. Endogenous activators, t-PA and urokinase have their own inhibitors, termed plasminogen activator inhibitors. Secondly, any circulating free plasmin produced by plasminogen activation is rapidly removed by antiplasmins, the most important being α_2-antiplasmin. Streptokinase is itself neutral-

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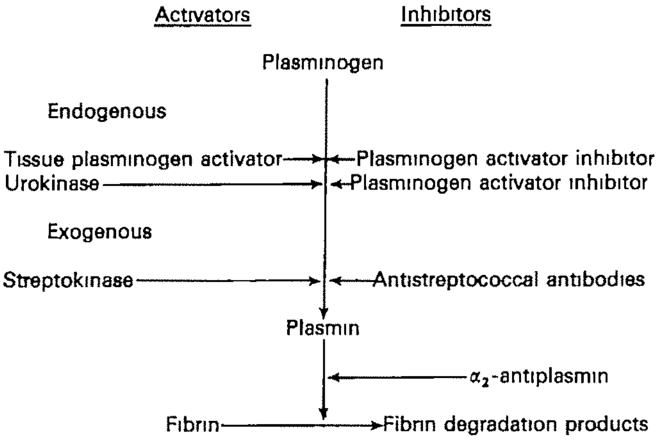
Activators
Inhibitors
Plasminogen
Endogenous
Tissue plasminogen activator
Urokinase
Plasminogen activator inhibitor
Plasminogen activator inhibitor
Exogenous
Streptokinase
Antistreptococcal antibodies
Plasmin
α_2-antiplasmin
Fibrin
Fibrin degradation products

Figure 1 *Pathways in fibrinolysis*

ized by plasma antistreptococcal antibodies, produced by prior streptococcal infection.

In 1958 Astrup proposed that there was a haemostatic balance between fibrinolysis and coagulation and that this homeostasis might be destabilized in certain pathological states[27]. Plasma fibrinolytic activity has indeed been shown to be reduced in patients with peripheral arterial disease[28]. Detailed reviews of the fibrinolytic pathways have been published elsewhere and investigation is still continuing in this field[29–31].

Before streptokinase was available for clinical use, non-specific proteases such as trypsin[32] and plasmin[33] were tried as thrombolytic agents without success. The first clinical trials were performed in 1958 when intravenous streptokinase was given to subjects with artificially induced superficial venous thrombophlebitis[34,35]. When early results were encouraging, streptokinase was tried on many patients with diverse thrombotic conditions, e.g. myocardial infarction, deep vein thrombosis, pulmonary embolism and acute peripheral arterial occlusion. One of the first reports on the clinical use of streptokinase described its use for acute limb ischaemia at King's College Hospital, London, in 1962. A patient with rethrombosis after femoral embolectomy received high-dose intra-arterial streptokinase, with good effect[36]. Two similar cases were reported from Glasgow[37]. Local haemorrhage was, however, a problem and this led to the belief that intravenous streptokinase would be a more suitable method of treatment for acute peripheral arterial occlusions.

Intravenous streptokinase

Two conditions were thought necessary for *in situ* clot lysis. First, it was important to overcome plasma streptococcal antibody resistance. This required a variable loading dose dependent on prior exposure to streptococci. Second, it was necessary to produce a systemic lytic state with a continuous infusion of streptokinase to supply free plasmin to overcome circulating antiplasmins. In early studies the initial dose was varied according to the measured plasma streptococcal resistance, the titrated initial dose. Exceeding this calculated dose provided no clinical benefit but increased bleeding complications[38]. Verstraete *et al.* showed that 500 000 units streptokinase neutralized all antistreptococcal antibodies in 82 per cent of the population, although 1·25 million units were required if a rate of 97 per cent was to be achieved[39]. In clinical studies the higher initial dose did not confer clinical advantage but increased haemorrhagic complications[40]. Debate continued with regard to the loading dose but most used a maintenance infusion of 100 000 units h^{-1} streptokinase. The addition of plasmin to intravenous streptokinase in an attempt to increase lysis simply increased systemic fibrinolysis and complications[41].

Despite the popularity of intravenous streptokinase in the 1960s, only a few centres reported detailed results[40,42–46]. Of 390 patients in published reports, successful lysis was recorded in only 39 per cent (*Table 1*). In another collected series of 438 cases (mostly from Germany), successful lysis was recorded in 46 per cent[47]. Haemorrhage was reported in 9–19 per cent of patients and was fatal in 4 per cent. A further 2 per cent developed non-fatal strokes. Thromboembolic complications were also frequent (9–11 per cent) and included embolization of lysing thrombus and acute myocardial infarction. The complications recorded were only the direct effects of infusion and in only one paper was the hospital mortality rate reported (32 per cent)[40]. In a later review Aldrich *et al.* documented a 3 per cent stroke rate during intravenous streptokinase therapy[48].

Several factors were found to influence the outcome of thrombolysis. The age of the occlusion was the most important, with improved lysis if the occlusion was less than 72 h old[40,43]. Fiessinger *et al.* stated that treatment was pointless for occlusions older than 8 weeks[45]. Patients with emboli were shown to benefit more than those with thromboses[45] and those with an initial neurological deficit were thought unsuitable[40,44,45]. Occlusions of proximal vessels such as the aorta (12 per cent) were less likely to be cleared, with lysis rates improving to 60 per cent in the popliteal and tibial arteries.

Improvements in vascular surgical techniques (especially using the embolectomy catheter) weighed against the limited clinical benefit and the attendant serious complications of

Table 1 *Results of intravenous streptokinase infusions in acute peripheral arterial ischaemia*

	Reference					
	Fiessinger *et al.*[45]	Amery *et al.*[40]	Schmutzler[42]	LeVeen and Diaz[43]	Samama and Conard[44]	Total
Year	1978	1970	1968	1972	1973	
No. of patients	194	68	65	35	28	390
Streptokinase dosage						
Loading (units)	Variable	500 000–1 000 000	200 000	250 000	500 000	
Maintenance (units h^{-1})	100 000	500 000	Variable	100 000	150 000	
No. of successful cases	57 (29)	21 (31)	44 (68)	16 (46)	15 (54)	153 (39)
Complications						86 (22)
Death	6	6	Unknown	5	1	18 (5)
Haemorrhage	18	16		–	–	34 (9)
Stroke	–	6		1	–	7 (2)
Thromboemboli	21	6		–	–	27 (7)

Values in parentheses are percentages

intravenous streptokinase and it never came into routine use. A recent survey, however, has shown that one-third of vascular surgeons in the UK who employ thrombolysis still occasionally use the intravenous route[49]. Intravenous streptokinase has been deemed appropriate treatment for selected patients with emboli or graft occlusions if surgery is not appropriate and intra-arterial lysis is not available[50]. Fiessinger, who has the largest series of patients treated with intravenous streptokinase, still uses the technique to 'rescue' patients after failed reconstructive surgery with benefit in 50 per cent[46], a similar result to that achieved by Fischer *et al.*[51]. A new method of streptokinase administration called 'burst therapy', in which high-dose (600 000 units) intravenous streptokinase is given over 1 h twice daily to prevent fibrinogen depletion, has been reported with good results in 12 patients[52].

A further development is the production of a new agent anistreplase (Eminase®, Beecham Pharmaceuticals, Welwyn Garden City, UK)[53]. This agent is a complex of streptokinase with plasminogen which produces direct plasminogen activation. Acylation of the active site of the plasminogen moiety prevents inactivation by antiplasmins. The complex is deacylated slowly having the clinical effect of increasing the half-life of streptokinase. The initial optimism of specific fibrin binding was unfortunately unfounded, although the complex remains a useful agent which may be given in intravenous bolus doses. It has become widely used in acute myocardial infarction Anistreplase has been investigated in acute limb ischaemia where 5 mg intravenous bolus doses (equivalent to 180 000 units streptokinase) were given every 8 h for up to 3 days. The clinical effects were no more impressive than when intravenous streptokinase was used and in both published reports haemorrhage was a significant problem[54,55]. Although anistreplase does not seem suitable for routine use in acute limb ischaemia, the concept of acylation is applicable to other fibrinolytic agents and other useful drugs may yet emerge.

Intra-arterial streptokinase

Dotter *et al.* are credited with the reintroduction of local intra-arterial fibrinolysis using catheter-directed infusions of low-dose streptokinase, one-twentieth of the previous systemic dose[56]. The aim was to produce the maximum thrombolysis at the site of the occlusion with the minimum of systemic effects The technique was largely ignored until Hess *et al.* published results of a series of 136 patients in which the recanalization rate was 69 per cent[57].

The basic technique has changed little since the description of Dotter *et al.* (*Table 2*), although some minor modifications are believed to have improved results. An intra-arterial catheter is positioned by the Seldinger technique so that the tip lies within the proximal part of the arterial occlusion. It is important that the tip is inserted into the thrombus to produce a *cul-de-sac* effect with a high local concentration of streptokinase and to prevent the drug from perfusing collaterals. A solution of streptokinase (5000 units h^{-1}) is infused via the catheter using a syringe pump. Regular arteriography is performed via the catheter which is advanced into residual thrombus as lysis occurs. When vessel patency is restored the catheter is withdrawn.

Occlusions above the inguinal ligament are approached from the contralateral groin whereas those below are usually more easily reached by antegrade femoral puncture. Simple 4–5 Fr polypropylene end-hole catheters are used. Aortic occlusions may be reached by the axillary or brachial routes, although there is the potential for cerebral embolism with this approach[58]

The time taken for recanalization varies between a few hours and 4–5 days and is mainly dependent on the length of the occlusion. The procedure may be performed in the radiology department, but if prolonged will need to be continued in either the intensive care unit or in a ward staffed by nurses used to caring for patients after vascular operations[59]. If a residual arterial stenosis is uncovered by recanalization, angioplasty may be performed at the time of catheter removal without harmful effects[60]. Removal of the catheter several hours after the streptokinase is stopped has been recommended[61] but may not be necessary. There may be further clinical improvement after the catheter is removed due to continued thrombolysis. Early rethrombosis is a risk after catheter removal and anticoagulation with heparin, and subsequently warfarin, has been recommended empirically. Antiplatelet therapy with aspirin has also been effective in preventing rethrombosis in both clinical[62] and experimental[63] situations.

Table 2 *Technique of local streptokinase infusion*

Procedure	Details
Angiography	Antegrade femoral puncture for femoropopliteal occlusion Contralateral approach for iliac occlusion 3–5 Fr polypropylene end-hole catheter Catheter inserted 1 cm into occlusion
Infusion	Streptokinase 5000 units h^{-1} ±heparin 250–1000 units h^{-1}
Monitoring	Haematological: fibrinogen and clotting studies every 12 h Angiography at least every 12 h with catheter advancement if appropriate
Catheter removal	When occlusion completely lysed and distal pulses restored After angioplasty, if residual stenosis uncovered If no improvement, either angiographic or clinical between angiography procedures
After thrombolysis	Intravenous heparin given to prolong APTT 2–3-fold for 5 days to prevent rethrombosis Subsequent long-term therapy either with warfarin or aspirin ±dipyridamole

APTT, activated partial thromboplastin time

Alterations in this basic technique have been proposed. An initial bolus of streptokinase does not appear to improve results[64]. Clot disruption may be important and the passage of a guidewire across the occlusion is associated with better results, probably reflecting the degree of organization of the thrombus[31]. A new technique of 'pulsed thrombolysis' induces clot disruption, and early results demonstrate increased speed of recanalization[65]. Lysis of clot by withdrawal of the catheter from distal to proximal may be more suitable for long occlusions than the method of advancement[60]. The addition of plasminogen to low-dose streptokinase does not improve results[66]. There is experimental evidence that combination with prostaglandin PGE_1 may enhance the effects of fibrinolytic agents[67].

The major published results of intra-arterial streptokinase therapy are shown in *Table 3*. Analysis of the collected data is difficult because of the diversity of patients treated. Patients with rest pain or claudication due to thrombosis, emboli, graft and postangioplasty occlusions have all received thrombolysis. In the collected series of 1849 patients the mean rate of successful lysis (although this has not been clearly defined) was 62 per cent[59,61,62,64,68–84]. Complications included major haemorrhage requiring blood transfusion in 4 per cent, minor haemorrhage in 10 per cent and a mortality rate of 3 per cent.

Hess *et al.* initially reported an early rethrombosis rate of 25 per cent, but a patency rate of 70 per cent after 1 year if the vessel was functioning 2 weeks after thrombolysis[57]. Long-term patency was stated to be 63 per cent after 5 years[62]. Lammer *et al.* reported a 10 per cent early rethrombosis rate, but claimed an 81 per cent patency after 2 years[70]. These results are comparable with those after vascular reconstruction. Long-term patency has been described, particularly in patients in whom an underlying cause for the occlusion, such as an arterial stenosis, has been uncovered and treated by angioplasty[85].

Table 3 *Results of low-dose intra-arterial streptokinase*

Reference	Year	No of patients	Successful lysis	Haemorrhage Minor	Haemorrhage Major	Death
Hess *et al.*[62]	1987	564	313 (55)	10	8	9
Allen *et al.*[68]	1989	202	165 (82)	35	2	29
Graor *et al.*[69]	1984	159	88 (55)	39	7	1
Lammer *et al.*[10]	1986	136	107 (79)	–	5	–
Walker and Giddings[61]	1988	70	52 (74)	–	4	5
Do-dai-Do *et al.*[59]	1987	69	49 (71)	–	3	–
Katzen *et al*[72]	1984	65	45 (69)	–	6	–
Wilms *et al.*[73]	1987	64	49 (77)	7	–	–
LeBolt *et al.*[64]	1988	60	28 (47)	9	5	1
Stiegler *et al.*[74]	1986	57	44 (77)	–	1	1
Becker *et al*[75]	1983	51	24 (47)	14	7	2
Stein *et al.*[76]	1987	50	18 (36)	–	–	
Mori *et al.*[77]	1983	45	22 (49)	15	4	1
Sicard *et al*[78]	1985	43	16 (37)	16	4	3
Sussman *et al*[79]	1984	40	23 (57)	4	1	1
Earnshaw *et al*[84]	1989	36	22 (61)	5	0	4
Lang[80]	1985	35	27 (77)	5	2	1
Kakkasseril *et al.*[81]	1985	35	15 (43)	7	6	–
Hurley *et al.*[82]	1984	34	19 (56)	16	2	1
Hamelink and Elliott[83]	1986	34	23 (67)	10	3	–
Total		1849	1149 (62)	192 (10)	70 (4)	59 (3)

Values in parentheses are percentages

Good long-term results have also been achieved following complete dissolution of arterial emboli[74] and in situations where the distal arterial tree is patent.

Hazards of intra-arterial streptokinase

A recent review identified the following complications: major haemorrhage 5 per cent, minor haemorrhage 15 per cent and stroke 1 per cent[86]. Some, although not all, bleeding complications have been related to plasma fibrinogen depletion[69]. Despite the low infusion concentration, systemic fibrinolysis occurs in about one-quarter of patients[60], but it is not particularly predictive of haemorrhage[77]. Fibrinogen depletion has been shown to be related to initial streptococcal antibody resistance[87], but variable dose regimens have not been established which reduce haemorrhagic complications. Serial measurement of fibrinogen or clotting profiles has not been demonstrated in a clinical study to reduce bleeding complications, although monitoring is advised by most clinicians. Haemorrhage has been reported through the interstices of knitted Dacron® (E.I. du Pont de Nemours and Company, Wilmington, Delaware, USA) grafts[88], and thrombolysis should not be used within 1 month of Dacron graft insertion. Failure of formation of neointima in Dacron grafts may render them at risk from this problem for ever.

Pericatheter thrombosis, due to stagnation of blood around the catheter, occurs in up to 26 per cent of patients[89]. Concurrent anticoagulation with intravenous heparin[72] or mixing low-dose heparin with streptokinase may reduce pericatheter thrombosis, although it has been suggested that the former method increases haemorrhagic complications[77]. An acceptably low pericatheter thrombosis rate has been recorded using concurrent infusion of 250 units h^{-1} heparin without major bleeding[60]. As far as the catheters themselves are concerned there are two schools of opinion. On one hand there is the use of small (3–5 Fr) end-hole polypropylene catheters. The other approach is to use a dual catheter system with streptokinase being perfused into the thrombus distally and heparin[90] (or urokinase[91]) being given at the proximal end of the catheter via a sheath. The latter method may be advantageous but leaves a larger arterial puncture site which may bleed later.

Distal embolization of fragments of lysing thrombus may worsen ischaemia but continued perfusion usually results in lysis of the emboli. If the limb is rendered critically ischaemic by distal embolization, without improvement after a further 4–6 h of streptokinase therapy, surgical thromboembolectomy must be considered before the limb becomes irreversibly damaged[76]. During lysis of iliac occlusions clot may embolize down the opposite limb due to a 'whirlpool' effect[92]. Embolic stroke has been reported due to detachment of intracardiac clot caused by systemic fibrinolysis. For this reason it has been suggested that thrombolysis should never be used for emboli unless an echocardiogram has demonstrated no intracardiac thrombus.

Arterial perforation during streptokinase infusion is a rare complication which prevents completion of treatment. It appears to be caused by a direct local effect on the arterial wall rather than catheter trauma[93].

Other infrequent complications include allergic reactions ranging from a rash to acute anaphylaxis or serum sickness due to prior sensitization with streptococci[94]. This is rare now as modern streptokinase is highly purified and it may be prevented by prior administration of 100 mg hydrocortisone. Pyrexia during thrombolysis is often stated to be due to allergy, but may in fact be due to release of pyrogens from revascularized muscle. Antipyretic therapy with paracetamol (not aspirin) is usually adequate treatment.

A second course of streptokinase within a few months of initial treatment may result in anaphylaxis and is not recommended because, if administered without event, there is no evidence that it will be effective due to prolonged high levels of antistreptococcal antibodies.

Revascularization of necrotic tissue can cause myoglobinuria and renal failure. The use of thrombolysis to enable a more distal amputation when ischaemic necrosis has already occurred should be deprecated[80].

Thrombotic complications, e.g. myocardial infarction and stroke, are associated with thrombolysis, despite systemic fibrinolysis. This may be due to a rebound relative fibrinolytic deficiency after thrombolysis[78], or simply to a manifestation of the underlying tendency to thrombosis. Streptokinase has been shown to increase platelet adhesiveness and to damage vessel intima during infusion[95].

Which patients are most suitable for thrombolysis?

Most clinicians recommend thrombolysis for patients who are unlikely to benefit from surgery or for those in whom operation carries a high risk. The severity of ischaemia has been shown to be the most important factor determining prognosis. The affected limb must be capable of withstanding a further period of ischaemia for the duration of thrombolysis. Patients with acute 'total' ischaemia including a neurological deficit should, therefore, be considered for urgent surgery[61]. Conversely, a good distal run-off[76] and an ankle/brachial systolic pressure index $>0{\cdot}25$[96] have been shown to be good prognostic signs Restoring patency to the distal vessels seems vital to limb salvage[59]. Short, recent occlusions are lysed more successfully than long, chronic ones[62,97], although the time element seems less important than when intravenous streptokinase was used[73] and occlusions up to 1 year old have been treated successfully[70].

The site of the obstruction has not been shown to have any bearing on outcome using local thrombolysis, but elderly patients are less likely to achieve limb salvage[84]. Embolic occlusions usually lyse more frequently than thromboses and a lysis rate of 77 per cent in 57 patients with emboli unsuitable for surgical embolectomy has been described[74]. This may be because embolic occlusions are largely composed of soft fresh secondary thrombus and the underlying vessels are often normal. Patients with embolic occlusions several days old may have a better chance of improvement with thrombolysis than surgery[62]. Distal occlusions, both thrombotic and embolic, can be successfully managed by thrombolysis[98]. Other suitable patients include those with emboli following myocardial infarction because they have a high mortality rate after surgery[61,99], patients with thrombosed popliteal aneurysms who have a high amputation rate due to run-off thrombosis[61,71,91,97–100], and young patients with short, isolated popliteal occlusions with the aim of restoring long-term patency to the native vessel. Local infusion of streptokinase into unselected patients with inoperable end-stage peripheral vascular disease has produced limited benefit[76].

Catheter-directed thrombolysis can be used for patients with unrelieved ischaemia following surgical embolectomy when there is residual clot in small distal vessels, although the risk of haemorrhage is increased[101]. Alternatively, an infusion of 100 000 units streptokinase given directly into the distal vessels at the time of surgery may clear residual thrombus[102–104]. Complications with this technique are reported to be infrequent.

There is controversy over the use of streptokinase for graft occlusions, with great variation in reported lysis rates from 30 to 90 per cent[97,105]. Impressive results have been published with urokinase[106] and t-PA[107], although others have not achieved as good results as with native vessel occlusions[64,108]. Graft thrombosis is often secondary to progression of distal disease and therefore patency is frequently not prolonged and may not save the limb. It has been argued that intra-arterial streptokinase administration is a useful initial manoeuvre which may demonstrate the underlying cause of graft thrombosis after which corrective surgery or primary amputation can be performed[105]. After thrombolysis of graft occlusions corrective surgery is required more frequently than after native vessel occlusions[99] but if a lesion can be found and corrected prolonged patency may be anticipated[105]. Thrombosed saphenous vein grafts have a poor response to surgical thrombectomy and are more suitable for thrombolysis than thrombosed prosthetic grafts[64,81]. The technique is, however, useful for thrombosed Dacron grafts[109]. In a single retrospective study comparing surgery with thrombectomy for graft occlusion, initial recanalization rates were similar, but long-term patency was better following thrombolysis[107].

Thrombolysis is contraindicated for patients at risk of haemorrhage. Guidelines were established for the use of intravenous streptokinase in thrombotic diseases in 1980[110]. The guidelines were designed for systemic thrombolysis and need not be so rigorously applied for low-dose intra-arterial therapy. It is prudent, however, not to treat patients within 2 months of a stroke or those with an obvious source of bleeding, e.g. peptic ulcer[60].

Which thrombolytic agent?

New agents are currently under investigation and a second generation of 'endogenous' fibrinolytic agents manufactured by recombinant DNA technology is available for fibrinolytic therapy.

Urokinase

Urokinase is an endogenous plasminogen activator initially isolated from urine. In the USA urokinase has been preferred to streptokinase, despite costing six times more[111], because improved lysis rates with fewer bleeding complications were reported in several (non-randomized) comparative studies[91,105,111–114]. High-dose intra-arterial urokinase infusions (4000 units $\text{kg}^{-1}\,\text{h}^{-1}$) were used in 129 patients with a lysis rate of 77 per cent, although only 59 per cent of vessels remained patent after 6 months[85]. Low-dose intra-arterial urokinase (37 500 units h^{-1}) was less satisfactory in 69 cases with a lysis rate of only 35 per cent and an amputation rate of 40 per cent[115]. In a similar group of patients, the addition of lys-plasminogen to low-dose intra-arterial urokinase improved the lysis rate to 85 per cent[58].

Tissue plasminogen activator

t-PA is normally produced by the vascular endothelium and is responsible for plasma fibrinolytic activity. It has the advantage of relative specificity for fibrin, with potential for action only at the site of recent thrombus deposition[31]. This might increase fibrin removal and yet minimize the side-effects caused by systemic fibrinolysis. However, this fibrin specificity might increase the risk of haemorrhage from other sites and be a less important factor when low-dose intra-arterial fibrinolysis is used. Infusions in human volunteers showed that t-PA had a very short half-life of 1·5 min but that the plasma fibrinolytic response was very variable, occasionally producing considerable fibrinogen depletion[116].

Graor *et al.* investigated the use of t-PA in 55 patients with acute peripheral arterial occlusions. Lysis occurred in 51 (93 per cent) patients, with clinical improvement in 48 (87 per cent)[117]. The infusions were required for a mean of only 4·7 h compared with several days in a previous series of similar patients treated with low-dose intra-arterial streptokinase by the same authors[69]. Although systemic fibrinolysis with reduction of plasma fibrinogen below 1 $\text{g}\,\text{l}^{-1}$ was seen in 24 per cent of the patients, the rate of haemorrhagic complications was low. A further study by the same group compared infusions of 0·1 and 0·05 $\text{mg}\,\text{kg}^{-1}\,\text{h}^{-1}$ t-PA and found that the lower concentration was equally effective but produced fewer systemic effects[118]. Other centres investigating t-PA have concluded that initial calculated infusion concentrations were too high and that low-dose infusions are equally effective[119,120]. In the UK the recommended concentration of t-PA for local thrombolysis is 0·5 $\text{mg}\,\text{h}^{-1}$ (Reference 121).

Published reports on intra-arterial t-PA have consistently shown lysis rates between 70 and 100 per cent[117–123]. In the only randomized trial the limb salvage rate was 75 per cent with t-PA compared with only 60 per cent with low-dose streptokinase, a significant improvement[122]. The speedier action of t-PA means that shorter infusions are required and makes it possible for patients with a neurological deficit to be treated when the limb is immediately at risk. Unlike streptokinase, t-PA has no immunological effect and can therefore be used on more than one occasion in the same patient[123]. Early rethrombosis after t-PA treatment might be reduced because, unlike streptokinase, t-PA has no effect on platelets[124]. There is experimental evidence of an improved lysis rate when heparin is used in association with t-PA[125]. In clinical studies haemorrhagic complications after t-PA have occurred with a similar frequency to that after streptokinase (and have included fatal strokes) despite the systemic effects being less pronounced[126]. This may be due to the excessive formation of fibrin degradation products by speedier fibrinogen degradation, the products themselves being anticoagulant. In a randomized trial, intravenous t-PA proved to be inferior to both intra-arterial t-PA and streptokinase for acute limb ischaemia[122].

t-PA may eventually supersede streptokinase but there is a large price difference. The cost of the thrombolytic agents to Bristol Royal Infirmary Pharmacy in April 1990 was £175 for 20 mg t-PA compared with £21 for 250 000 units streptokinase. Cost–benefit analysis of thrombolysis will be important because the high cost of patients after amputation may justify the use of expensive thrombolytic agents[127]. Until then, specific indications for t-PA remain few but include patients who are allergic to streptokinase or who have received streptokinase within the previous 2 years.

Other new agents

These include single-chain urokinase plasminogen activator (scu-PA), the inactive precursor of urokinase. Unlike urokinase, scu-PA has a high affinity for fibrin which it then activates. It is also produced by recombinant technology but has yet to be investigated in acute limb ischaemia[31].

A recent discovery is that the combination of low doses of t-PA and scu-PA cause greater lysis than would be expected from each agent alone[128]. This synergism may occur because t-PA and scu-PA have different biological mechanisms. It can be demonstrated *in vivo*, but its clinical significance is as yet uncertain[129].

Urokinase has been combined with fibrin-specific monoclonal antibodies to produce a complex with high fibrin specificity which *in vitro* shows a 100-fold increase in thrombolysis when compared with an equivalent dose of urokinase alone[130]. Combinations of available thrombolytic agents and monoclonal antibodies may produce a range of fibrinolytic drugs for the future.

Roles of thrombolysis and/or surgery in acute limb ischaemia

It is not acceptable to regard thrombolysis and surgery as competitors because each method has advantages and, on occasion, both may be suitable. Thrombolysis is now a genuine alternative in the management of acute limb ischaemia[124,131].

The results of surgery for iliofemoral arterial emboli are unlikely to be improved upon, particularly if embolectomy is reserved for patients with a likely embolic source, an ischaemic history of less than 72 h and no prior claudication[132]. However there must be no reluctance to proceed to vascular reconstruction (or thrombolysis) if embolectomy fails[9]. Urgent surgery also remains the treatment of choice for acute 'total' ischaemia where there is a neurological deficit.

In patients unlikely to benefit from surgery, particularly those thought to have acute thrombosis, thrombolysis has been shown to produce worthwhile clinical results. Using intra-arterial streptokinase is demanding, time consuming and gives the best results only with experience[133]. Co-operation is required between surgeons, radiologists and haematologists. The materials and drugs are expensive and the technique has not been shown to reduce hospital stay. At least one-quarter of patients will not benefit from thrombolysis, and surgery may subsequently be required. The use of surgery after thrombolysis is probably safer than *vice versa* when haemorrhagic complications are frequent. The combination of surgery and thrombolysis may also take the form of intraoperative lysis of residual thrombus or operative placement of catheters for subsequent streptokinase infusion. The main disadvantage of thrombolysis is that the limb must be capable of withstanding a further period of ischaemia while recanalization occurs, although t-PA with its speedier action may supersede streptokinase and extend the role of thrombolysis.

Table 4 *Guidelines for the management of patients with acute limb ischaemia*

	Suitable for thrombolysis
Specific indications	Acute thrombosis with poor run-off Popliteal/tibial occlusion Delayed emboli Thrombosed popliteal aneurysm
Medical indications	Elderly patients unfit for major vascular reconstructive surgery
Possible indications	Short popliteal occlusion in young patients Acute-on-chronic thrombosis with run-off suitable for either surgery or thrombolysis
	Not suitable for thrombolysis
Specific indications for surgery	Recent iliofemoral emboli Acute 'total' ischaemia including a neurological deficit
Specific contraindications	Recent stroke within 2 months Increased risk of haemorrhage
Relative contraindications	Recent surgery within 1 week

A guide to the relative roles of surgery and thrombolysis in acute ischaemia can be formulated from the open clinical studies (*Table 4*). Further information is required, particularly for patients suitable for either method, which can be provided only by randomized studies. The trials will have to be large and well designed because acute ischaemia is a diverse condition. Standardization of reporting data is important for comparisons between studies, and guidelines are required[134]. Evaluation of new fibrinolytic methods will have to proceed in parallel with other new non-surgical techniques for treating acute limb ischaemia such as percutaneous aspiration thromboembolectomy[135].

Apart from embolectomy, operations for acute limb ischaemia should no longer be the testing ground for junior surgeons. Failed embolectomy without further action is not acceptable. There must be the willingness and expertise available to proceed with vascular reconstruction at the same operation[131]. Acute limb ischaemia is no longer the business of every general surgeon[136] but the domain of the committed vascular surgeon with the capability to select surgical or non-surgical treatment for the patient and with access to assistance from skilled radiological colleagues. Currently this remains an ideal, although centralization of vascular services in Edinburgh seems to have improved the outcome from acute limb ischaemia compared with historical controls[20]. Until this ideal can be achieved patients with a firm diagnosis of embolism[132] should have an embolectomy and the remainder should have arteriography and assessment by a surgeon with knowledge of, and access, to the optimal current surgical and non-surgical techniques.

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Regeneration of the spleen and splenic autotransplantation

R. J. Holdsworth

Department of Surgery, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK

Correspondence to:
Mr R. J. Holdsworth

This paper reviews the subject of regeneration of the spleen and discusses the role of splenic autotransplantation following splenectomy for trauma.

Awareness of the possibility of an increased incidence of infection following splenectomy has led to a reassessment of the indications for removal of the spleen, particularly following traumatic splenic rupture. An increasing number of reports suggest that the spleen should be conserved if possible[1–7]. However, in some cases of splenic trauma the spleen is shattered beyond repair and total splenectomy becomes inevitable. Methods used to minimize pneumococcal infection following splenectomy include prophylactic antibiotic therapy and antipneumococcal immunization. In addition, when the spleen is removed following trauma, splenic tissue can be reimplanted into the peritoneal cavity where it will regenerate – the technique of splenic autotransplantation.

For over 100 years it has been appreciated that the spleen has the capacity to regenerate. Griffini and Tizzoni in 1883[8] were the first to describe areas of spontaneous splenic regeneration in the peritoneum of dogs which had undergone splenectomy. Within a few years a similar occurrence had been noted in humans[9,10]. The term 'splenosis' was first suggested by Buchbinder and Lipkoff in 1939[11] to describe areas of spontaneous splenic regeneration in the peritoneum in people who had their spleen removed for trauma. In 1978, Pearson *et al.*[12] reported that following splenectomy for traumatic splenic rupture up to 50 per cent of people develop areas of splenosis, and they advanced the theory that splenosis could be an explanation for the relatively low incidence of postsplenectomy sepsis seen after trauma in adults. This led to the conclusion that deliberate splenic autotransplantation at the time of splenectomy might convey a similar benefit.

The topics of splenic conservation and the effectiveness of immunization have recently been reviewed[4,7]. The aim of this paper is to put the subject of splenic autotransplantation into perspective.

Histological regeneration of the spleen

Tavassoli *et al.*[13] described the histological sequence of events in the regeneration of subcutaneous splenic autotransplants in rats. Initially, necrosis of the tissue occurs within the first 4 days; only the very edges of the tissue remain viable. During the period of necrosis the tissue becomes hypocellular with a loss of the lymphoid elements and only the rudimentary connective tissue structure remains[13,14]. Regeneration commences in the outer layer with a differentiation of the connective tissue lattice into splenic reticular cells. Vascular regrowth can be seen within 8 days with lymphocytes around the primitive vessels[14] The white pulp differentiates first and is distinct by the fifth week. The weight of the tissue returns to normal by the fifth week although smaller implants can regenerate faster. Regenerated fragments appear histologically normal with distinct areas of red and white pulp. Although a true capsule with trabeculae is absent, the fragments are surrounded by a dense layer of connective tissue containing many blood vessels, some of which occasionally penetrate into the tissue giving rise to short trabeculae-like structures[13].

Sites for splenic regeneration

Splenic tissue can regenerate in almost any part of the body but the intra-abdominal and subcutaneous locations are usually preferred. The peritoneal cavity is the favoured site not only for convenience but also because this site provides the greatest chance of graft regeneration. This almost certainly relates to the rich blood supply of the peritoneum which can maintain the grafts by diffusion during the time required for neovascularization[15]. A considerable number of animal experiments have shown satisfactory regeneration of grafts placed in the peritoneum, whether by placing the spleen into omental pouches or simply by dropping fragments into the peritoneum to reseed by 'splenosis'[15–37]. Retroperitoneal implants have also been shown to regenerate well[38].

The technique of placing spleen into omental pouches is preferred to retroperitoneal implantation because there is an opinion that it is important to establish venous drainage via the portal circulation. This most closely resembles the normal anatomical position of the spleen and the liver may co-operate with the spleen in antigen processing[15].

The other favoured location for placing splenic autografts is subcutaneous tissue; however, the ability of spleen to regenerate in this site is more variable. Some authors have reported normal but slower regeneration than with intra-abdominal implants[13,15,17,19,39] whereas others have found that this method is largely unsuccessful[18,32]. The most likely explanation for these discrepancies is the more variable blood supply in the subcutaneous tissue which is required to maintain the grafts before revascularization.

The desire to place autotransplanted spleen so that it drains via the portal circulation has led to the idea of seeding splenic tissue into the liver via transportal injection. This technique has been shown to work experimentally in two studies[40,41] although additional experiments using the same technique were unsuccessful[23,28].

Why does the spleen regenerate?

Tavassoli[17] postulated that regrowth of the spleen was governed by a humoral factor which acted as a negative feedback inhibitor of growth. Whether or not this humoral factor exists, and whether it is a direct feedback from a substance produced locally by the spleen or regulated through an intermediary system, remains unknown. The evidence for a humoral factor is twofold. Firstly, studies have demonstrated that splenic fragments fail to grow if the spleen is also present[42,43]. Secondly, Tavassoli[17] showed that there is a limit to the size to which the splenic fragments will grow. He suggested that there is an initial unit volume of the animal's own spleen and that when the fragments have regenerated to this amount they fail to increase any further. The weight to which fragments regenerate is independent of the initial weight implanted. Against this latter argument are the data of Pabst and Karman[21] who found that not only is the end-regenerated

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mass independent of the amount initially implanted, but also that only a small proportion of the total mass implanted will regenerate.

In the absence of a proven humoral factor regulating splenic regrowth an alternative possibility can be suggested. When spleen is reimplanted the tissue becomes hypocellular with disappearance of the lymphoid tissue. The lymphoid elements reappear only at a late stage of regeneration following the period of revascularization[13,14]. Tavassoli *et al.*[13] suggested that the new lymphoid elements differentiated from tissue that remained viable in the very periphery of the implant. Alternatively, once the connective tissue network has been revascularized, it is possible that the lymphoid tissue is replenished from the circulating lymphocyte pool[14]. The latter explanation may be a distinct possibility, particularly as it is now appreciated that the lymphoid elements of the normal spleen are constantly recirculating[44,45]. In favour of this latter theory would also be the findings of Patel *et al.*[32] who reported that omental pouch implants created using sliced spleen had a normal splenic structure whereas implants created by splenosis had a rather indistinct separation of areas of red and white pulp indicating that the framework of the implant was more distorted. This theory may also explain why attempts at implanting spleen into the liver using fragmented, homogenized spleen have been disappointing: the basic connective tissue framework is lacking[23,28,40,41].

When the spleen regenerates it appears histologically normal. The immunoarchitecture of human spleen can be studied using monoclonal lymphocyte markers and different zones of lymphocyte differentiation can be identified[46]. This type of immunohistology has never been undertaken on regenerated spleen and additional investigations on regenerating fragments may provide a clue as to the source of the lymphocytes appearing in regenerated splenic fragments.

Splenic autotransplantation in humans

There are many reports of spontaneous regeneration in humans as a result of splenosis following splenic trauma[12,47–53] and it has been suggested that following traumatic splenectomy 50–66 per cent of patients have evidence of spontaneous splenic regeneration[12,49,51].

Despite considerable concern over the risks of post-splenectomy infection, the well documented ability of spleen to regenerate, and the simplicity of carrying out the procedure, intentional splenic autotransplantation appears not be a widely undertaken procedure. Remarkably few reports of splenic autotransplants appear in the literature[1,4,54–61]. The largest series is of 43 patients reported by Moore *et al.* in 1984[55]. It should be noted that this series almost certainly includes the 23 cases reported by Millikan *et al.* in 1982[1]. *Table 1* summarizes the patients and the techniques used.

The majority of authors placed implants into omental pouches but there is no uniform number or size of implants. Methods range from the use of homogenized spleen[56,58] through the use of small cubes[61], thin and thick rectangular slices of different dimensions[1,4,55,57], to thin slices (approximately 3 mm) of the whole of the middle of the spleen[54]. Even

Table 1 *Summary of reports of methods of splenic autotransplantation in humans*

Reference	No. of patients	Indication for splenectomy	Site of implant	Method of implantation	Follow-up studies
Patel *et al.* (1981)[54]	4	Blunt trauma	Omental pouch	2 slices of whole spleen 3 mm thick	Scintiscans IgM levels Complement C3 Platelets
Velcek *et al.* (1982)[57]	3	Blunt trauma in children	Omental pouch	15–20 slices 15 × 15 × 2 mm	Scintiscans Antipneumococcal antibody levels IgM levels
Millikan *et al.* (1982)[1]	23	Blunt and penetrating trauma	Omental pouch	5 slices 20 × 20 × 5 mm	Scintiscans IgM levels Platelet count
Moore *et al* (1984)[59]	43	Blunt and penetrating trauma	Omental pouch	5 slices 40 × 40 × 3 mm	Scintiscans IgM levels Platelet count
Dung *et al.* (1984)[58]	9	Blunt trauma	Omental pouch	Homogenized spleen 50–100 g total	^{99}Tc-labelled RBC scintiscan Lymphocyte subsets
Nielsen *et al.* (1984)[56]	14	Trauma (8) Vagotomy (6)	Omental pouch	Homogenized spleen in 10 cm^3 pouches 1/3 total spleen	^{99}Tc-labelled RBC scintiscan Blood films IgG, IgA, IgM levels Platelets
Nicholson *et al.* (1986)[61]	6	Chronic pancreatitis	Omental pouch	2–3 mm cubes 30–50 g total	^{99}Tc-labelled tin scintiscan ^{99}Tc-labelled RBC scintiscan Blood films Platelets
Traub *et al* (1987)[60]	7	Blunt trauma	Extraperitoneal pouch	25–30 g thinly sliced spleen	^{99}Tc sulphur colloid scintiscan Platelet count Blood films ^{51}Cr-labelled erythrocyte clearance
Büyükünal *et al.* (1987)[4]	16	Blunt trauma	Omental pouch	2–4 slices 30 × 50 × 5 mm	Scintiscans Blood films IgG, IgA, IgM levels Complement C3, C4 Lymphocyte subsets Opsonic activity

Ig, immunoglobulin; RBC, red blood cells fragments as large as 30 × 40 × 120 mm and weighing 50 g have been reimplanted in the peritoneum, apparently successfully[59]. Only Traub *et al.*[60] have reported successful extraperitoneal implants in humans Proof of successful regeneration is usually confirmed by either scintiscan, normal platelet numbers or a restoration of the peripheral blood film to normal.

Reported complications include a case of postoperative intestinal obstruction[4] and a postoperative subphrenic abscess[56], although neither case indicated whether or not the complication was directly due to the implant. Intestinal obstruction, chronic anaemia and torsion are also reported as complications of areas of spontaneous splenosis[4,62,63]. Theoretically, it would seem unwise to implant tissue in the presence of gross intraperitoneal contamination due to coexistent bowel damage. The ischaemic nature of the implants may act as a source for subsequent abscess formation; this complication has also been reported[64]. Nevertheless, Moore *et al.*[55] had a large number of patients with associated peritoneal contamination and felt that subsequent abscess formation was not a problem.

Functional ability of regenerated splenic tissue

There is now a considerable amount of evidence that regenerated splenic tissue can restore the filtering functions of the spleen. People with regenerated spleen have a reduction in the numbers of circulating pitted erythrocytes and approximately 50 per cent have a completely normal blood picture[12,47,48] However, improvement in the blood film is not a universal finding and the blood picture may remain unchanged even in the presence of splenic regeneration[49]. Platelet numbers have also been shown to be within the normal range after transplantation in both humans and experimental animals[1,20,54–56]. It is not surprising that splenic regeneration corrects the blood picture after splenectomy in view of the ability to detect regenerated splenic tissue by scanning with ^{99}Tc-labelled heat-damaged erythrocytes[15,47,48,56,57].

Splenectomy is frequently associated with a reduction in the amount of total circulating immunoglobulin M and normal levels of this immunoglobulin fraction are widely reported in those with regenerated spleen[1,4,48,49,54,56,57]. This is the only proven immunological role that is restored by reimplantation and there is considerable debate regarding other immunological parameters. Whether lymphocyte function is normal after reimplantation is certainly not clear. Dürig *et al.*[58], in probably the best paper on the subject, commented that there is a persistent B-cell lymphocytosis with normal T-cell numbers as a result of regenerated spleen, although normal T-lymphocyte and B-lymphocyte numbers have been reported elsewhere[4,50]. The immunoglobulin G secretion by lymphocytes *in vitro* is also reported as reduced in patients with splenosis, and this reduction is independent of the degree of splenic regeneration[48]. It should be added that there is some debate regarding the exact effect of splenectomy on lymphocyte numbers and function[48,58,65–69] and there is insufficient information available from which to draw conclusions regarding the ability of regenerated spleen to function normally at a cellular level.

A further consideration about the functional ability of regenerated spleen concerns the ability to produce antibody A number of studies have shown that there is a partial ability to synthesize antibody against autologous erythrocytes although this is rarely as good as that seen in sham operated animals[18,19,70,71]. Of more relevance to the human state following splenectomy is the immune response to pneumococcal immunization. Although Velcek *et al.*[57] did find a good response to immunization in three patients following transplantation, Kiroff *et al.*[51] found that in 21 patients with proven splenosis responses to pneumococcal immunization remained poor irrespective of the degree of splenic regeneration.

Many additional factors which are reported to be abnormal following splenectomy are also claimed to be restored by splenic autotransplantation. These include circulating autoantibodies[52], levels of the phagocytosis-stimulating α_2-glycoprotein, fibronectin[72], leukokinin levels and opsonic activity[73,74]. Another report claimed that altered pulmonary macrophage function as a consequence of splenectomy is restored to normal within only 6 days of 10 per cent autotransplantation[75,76] However, it is unlikely that this effect is the result of splenic regeneration because the autotransplanted fragments would still be undergoing necrosis after such a short period following transplantation.

Does reimplanted spleen protect against infection?

This is the crucial question when considering postsplenectomy sepsis. There is very little evidence to support any positive protective effect of regenerated spleen with respect to the later development of infection. The only available data from which this question can be answered are case reports of infection in the presence of regenerated spleen and the results of experimental animal studies.

Postsplenectomy sepsis in the presence of splenosis

At least 14 cases of overwhelming postsplenectomy infection are recorded in people with evidence of ectopic or regenerated splenic tissue; details of these cases are summarized in *Table 2*[77–86]. These were all fatal infections and evidence of splenic regeneration was discovered only at autopsy.

Ten infections were pneumococcal, two were meningococcal[85], one was due to *Haemophilus*[78] and in one case the organism was unidentified[77]. The youngest patient was 4 years old[78], but most were young adults. Seven patients had evidence of disseminated intravascular coagulation and ten had evidence of adrenal haemorrhage Eleven infections occurred 3 years or more after splenectomy. All the patients had fulminating illnesses and died within 36 h of the first symptom.

It must be stressed that these fatal cases do not exclude the possibility of splenic regeneration being protective, because all the patients with this fortunate outcome would remain undetected. The high rate of spontaneous splenosis, approaching 50 per cent, suggested by Pearson *et al.*[12] has been advanced as a possible explanation for the low incidence of postsplenectomy sepsis seen after splenectomy for trauma.

Residual or regenerated splenic tissue itself does not guarantee protection against sepsis. The quantity of regenerated spleen may be of relevance, although a case report of a fatal pneumococcal septicaemia in an 8-year-old child in the presence of 92 g regenerated spleen suggests that even large amounts of regenerated spleen may not be of any benefit[84].

Experimental studies on the protective effect of regenerated spleen

Laboratory evidence for a positive protective effect conferred by autotransplanted spleen against pneumococcal infection is controversial. Broadly speaking there are two types of animal experiment, those that measure mortality as an endpoint and those that simply measure changes in the blood clearance of organisms. The results of the principal experiments are summarized in *Table 3*[23–40] One criticism of much of this work is the use of a wide variety of different experimental animals, organisms, infecting routes, dosages and methods of autotransplantation from which it is difficult to make direct comparisons

Only Patel *et al.*[31] have shown in animal studies that autotransplantation has a positive protective effect (overall survival rate: transplanted 89 per cent; splenectomy 52 per cent); Dawes *et al.*[25] demonstrated a partial protective effect (overall survival rate: transplanted 36 per cent; splenectomy 4 per cent). A number of studies have documented a short-term protective effect for up to 48 h[15,22,34–36,38]; however, the long-term mortality rate was as high as that seen after total splenectomy. This unchanged long-term mortality

Table 2 *Summary of case reports of fatal postsplenectomy infection in patients with evidence of residual or regenerated splenic tissue*

	Age (years)						
Reference	At operation	At infection	Sex	Indication for splenectomy	Type of infection	Duration of illness*	Post-mortem findings
Erickson *et al* (1968)[77]	6	7	F	Dermoid cyst	Septicaemia (organism unknown)	4 h; ADR, DIC	1 cm accessory spleen
Singer (1973)[78]	2	4	M	Trauma	*Haemophilus* septicaemia	ADR	15 g splenosis
Sculley *et al.* (1975)[79]	13	23	M	Trauma	Pneumococcal septicaemia and meningitis	12 h; DIC	15 g splenosis, largest 3·5 cm in diameter
Balfanz *et al.* (1976)[80]	5	8	F	Trauma	Type 22 pneumococcal septicaemia	22 h, ADR	1·5 cm accessory spleen
Gopal and Bisno (1977)[81]	4	11	F	Trauma	Pneumococcal septicaemia	36 h	Several ectopic spleens, largest 12 g in weight
	17	27	M	Trauma	Pneumococcal septicaemia and meningitis	36 h; ADR, DIC	4 g accessory spleen
Reay and Nakonechny (1979)[82]	16	19	F	Trauma	Pneumococcal septicaemia	Sudden, ADR, DIC	Splenosis
	17	21	M	Trauma	Pneumococcal septicaemia	<1 h; ADR	Splenosis
Sher *et al.* (1979)[83]	12	29	M	Trauma	Pneumococcal septicaemia	6 h; DIC	Two areas of splenosis on liver surface
Rice and Jones (1980)[84]	4	12	F	Trauma	Pneumococcal septicaemia	9 h	100 areas of splenosis 2–4 mm in diameter, 3 g total weight
	10	14	M	Trauma	Pneumococcal septicaemia	22 h, ADR, DIC	42 g splenosis and 4·5 cm splenunculus, 92 g total weight
Holmes *et al.* (1981)[85]	22	27	F	Trauma	Meningococcal meningitis	26 h; ADR, DIC	25 g splenosis
	13	17	F	Trauma	Meningococcal meningitis	24 h, ADR	Splenosis
Moore *et al.* (1983)[86]	61	61	F	Trauma	Pneumococcal septicaemia	36 h, ADR	Five regenerated omental transplants, also vaccinated

* Duration of illness time given from first symptom to death; ADR, evidence of adrenal haemorrhage; DIC, disseminated intravascular coagulation

rate (at 10–14 days) in experimental infections has also been reported in a number of other studies[16,23,27,40].

In terms of clearance of bacteria from the blood, pneumococci can certainly be detected in sections of autotransplanted spleen[38]. However, only one study reports that blood clearance of pneumococci is complete in animals with omental implants[32]. One further study reports improved but incomplete clearance[37]. Many studies in contrast report that autotransplanted spleen has no effect on bacterial clearance compared with animals with a total splenectomy[26,35,36,39].

In selected studies immunization has been used in conjunction with autotransplantation and any improvement in survival is due to inoculation rather than splenic regeneration[25,35,36] Immunization also improved pneumococcal clearance in autotransplanted animals, but improved clearance resulted from increased uptake in the liver rather than in the regenerated fragments[35].

Pneumococcal infections are usually acquired via the respiratory tract and, to assess the true protective effect of autotransplanted tissue against pneumococcal infection, this route should be used to infect the animals. In this context the work of Dickerman *et al.*[33] is often quoted as providing irrefutable evidence for an increased protective effect conferred by autotransplanted spleen. However, although the protection offered by the autotransplanted spleen (70 per cent mortality rate) was improved compared with the total splenectomy group (100 per cent mortality rate), the mortality rate within the sham operated group was also over 70 per cent. Similarly, Livingstone *et al.*[28,29] also demonstrated improved protection againt type 3 pneumococcus given by intratracheal injection. However, once again, their control group had a 75 per cent mortality rate and all animals died from pneumonia. This is unlike the overwhelming septicaemia seen in clinical situations of postsplenectomy sepsis. In all these experiments the high mortality rate in the control groups must cast doubt upon the validity of these findings and the interpretation of the results

In conclusion, only the work of Patel *et al.*[31,32] has shown a positive protective effect in terms both of improvement in survival and of bacterial clearance associated with regenerated spleen; autotransplants created by slicing spleen in omental pouches was the only method that conferred any benefit. Results for autotransplants created from minced spleen in the omentum, or placed subcutaneously, or created by splenosis were no better than those for the total splenectomy group[32]. The majority of the studies show at best short-term benefits which produce marginally better results than those for splenectomized animals, but within 72 h these benefits are lost.

Autotransplantation *versus* splenic conservation

Conservation of the spleen is now the preferred method of dealing with splenic trauma. Techniques such as partial splenectomy, splenic repair and splenic artery ligation achieve a salvage rate of over 80 per cent in splenic trauma[2,4,5]. Splenic conservation is based on the concept of maintaining the normal vascular supply to the spleen. In experimental studies using a 50 per cent hemisplenectomy with conservation of the blood supply, the blood clearance of pneumococci is only marginally

Table 3 *Summary of reports of experimental studies of protective effect of splenic autotransplantation in animals*

Reference	Animal	Transplantation technique	Infecting organism	Infecting route	Infecting dose (organisms/ml)	Summary of results
Mortality studies						
Schwartz *et al.* (1978)[27]	Sprague-Dawley rats	Homogenized spleen by splenosis	Type 25 *Pneumococcus*	Intravenous	$4\cdot0\times10^{3}$ – $4\cdot0\times10^{8}$	No improvement in LD_{50} compared with total splenectomy group
Dickerman *et al* (1979)[33]	Swiss white mice	IP splenosis using spleen slices	Type 3 *Pneumococcus*	Aerosol inhalation	$2\cdot5\times10^{9}$	All animals died from pneumonia Mortality rate: splenectomy (100%), control (85%), transplant (75%)
Whiteside and Thomas (1979)[23]	Sprague-Dawley rats	i) Extraperitoneal ii) Intraperitoneal	Type 2 *Pneumococcus*	Intraperitoneal	10^{0}–10^{8}	No improvement in LD_{50} due to either transplant compared with splenectomy group
Tesluk and Thomas (1979)[34]	Sprague-Dawley rats	Not specified	Type 2 *Pneumococcus*	Intravenous	$5\cdot0\times10^{2}$ – $5\cdot0\times10^{8}$	Marginal improvement in LD_{50} in transplanted animals but not as good as controls
Patel *et al.* (1982)[31]	Sprague-Dawley rats	Omental pouch using slices	Type 25 *Pneumococcus*	Intraperitoneal	$2\cdot0\times10^{7}$	Apparent protective effect Mortality rate. splenectomy (48%), control (0%), transplant (11%)
Oakes *et al.* (1982)[40]	Lewis rats	Transportal into liver	Type 25 *Pneumococcus*	Intravenous	$1\cdot0\times10^{5}$	Mortality rate. splenectomy (91%), control (59%), transplant (88%)
Livingstone *et al.* (1983)[28]	Sprague-Dawley rats	IP slices in mesentery and subcutaneous	*Pneumococcus* serotype unknown	Intratracheal	$5\cdot0\times10^{7}$	Mortality rate: splenectomy (92%), control (76%), IP transplant (86%), subcutaneous implant (96%)
Livingstone *et al.* (1983)[29]	Sprague-Dawley rats	Diced spleen i) Mesentery ii) Portal injection	Type 3 *Pneumococcus*	Intratracheal	$5\cdot0\times10^{7}$	Mortality rate: splenectomy (100%), control (75%), peritoneal transplant (84%), portal transplant (91%)
Malangoni *et al.* (1985)[30]	Sprague-Dawley rats	Omental pouch 50% of spleen	Type 2 *Pneumococcus*	Intraperitoneal	$1\cdot0\times10^{5}$	Mortality rate. splenectomy (92%), control (0%), transplant (88%)
Clearance studies						
Weis *et al.* (1979)[39]	Sprague-Dawley rats	Subcutaneous (200 mg)	Type 25 *Pneumococcus*	Intravenous	$1\cdot0\times10^{6}$	No improvement in blood clearance of bacteria due to transplant
Brown *et al.* (1981)[26]	Guinea-pigs	IP splenosis using splenic fragments	Type 12 *Pneumococcus*	Intravenous	$1\cdot0\times10^{8}$	No improved clearance of bacteria compared with total splenectomy group
Horton *et al* (1982)[37]	New Zealand white rabbits	Retroperitoneal using diced spleen	Type 3 *Pneumococcus*	Intravenous	$4\cdot0\times10^{6}$	Improved clearance in transplant group compared with splenectomy but not as good as control group
Patel *et al.* (1986)[32]	New Zealand white rabbits	i) Slices in omentum ii) Homogenized in omentum iii) Homogenized by splenosis iv) Sliced subcutaneously	Type 25 *Pneumococcus*	Intravenous	$1\cdot0\times10^{7}$	Blood clearance measured Very poor in total splenectomy Complete in 2 h in controls Complete in 3 h in omental slice transplants Partial clearance in both homogenized transplants No clearance in subcutaneous group

Combined studies						
Cooney *et al.* (1979)[36]	Sprague-Dawley rats	Four equal retroperitoneal slices	Type 1 *Pneumococcus*	Intravenous	$3{\cdot}3 \times 10^4$	Clearance slightly improved in transplant compared with splenectomy group but not as good as sham control Mortality rate: splenectomy (95%), control (0%), transplant (95%)
Cooney *et al.* (1979)[35]	Sprague-Dawley rats	Retroperitoneal slices	Type 1 *Pneumococcus*	Intravenous	$1{\cdot}5 \times 10^3$ (non-immunized)	No improved clearance of bacteria compared with total splenectomy group Mortality rate: splenectomy (100%), control (0%), transplant (90%)
					$6{\cdot}5 \times 10^5$ (non-immunized)	Mortality rate: splenectomy and transplant both 100%, control (0%)
					$6{\cdot}5 \times 10^5$ (immunized)	No mortality in all groups
Moxon and Schwartz (1980)[24]	Sprague-Dawley rats	IP splenosis: homogenized spleen	*Haemophilus influenzae*	Intranasal	$3{\cdot}0 \times 10^8$	Bacteraemia improved and delay in development of meningitis in transplanted animals but not as good as controls Mortality rate: all control and transplanted animals survived but 70% of splenectomy group died
Fasching *et al* (1980)[38]	Sprague-Dawley rats	Retroperitoneal slices	Type 1 *Pneumococcus*	Intravenous	10–20 (non-immunized)	At low challenge dose splenectomy and transplant animals developed increasing bacteraemia Mortality rate: splenectomy (95%), control (0%), transplant (85%)
					$1{\cdot}0 \times 10^7$ (immunized)	All groups responded to immunization Mortality rate: splenectomy (70%), control (0%), transplant (30%)
Dawes *et al* (1985)[25]	Sprague-Dawley rats	Diced spleen in omental pouches	Type 2 *Pneumococcus*	Intraperitoneal	$1{\cdot}0 \times 10^5$ (non-immunized)	Partial protective effect Mortality rate: splenectomy (96%), control (10%), transplant (64%)
					$1{\cdot}0 \times 10^5$ (immunized)	All groups responded to immunization Mortality rate: splenectomy (19%), control (0%), transplant (10%)

IP, intraperitoneal, LD_{50}, dose at which 50 per cent of animals die less efficient than in sham operated controls, with an associated reduction in mortality rate from experimental pneumococcal infections. In these studies hemisplenectomy was considerably superior to autotransplantation in terms of blood clearance and survival[16,17,34,35,37]. If the spleen is left *in situ* and the splenic artery is ligated, the rate of clearance of pneumococci is considerably reduced but not to the same extent as seen after total splenectomy[37,87]. Despite this reduced blood clearance of organisms there is still an improved survival rate from experimental pneumococcal infection compared with that in animals with a total splenectomy[87]. In the one study that compared splenic artery ligation with autotransplantation, the blood clearance was identical in both groups and both were inferior to hemisplenectomy with conservation of the blood supply[87].

The blood flow in regenerated splenic fragments does not approach that seen in the normal spleen on a weight to weight basis[33,37]. Therefore, not only is the filtering function of regenerated spleen reduced but so also is the facility for antigen recognition and response to polysaccharide antigens[36]. The presence of an intact vascular supply and normal splenic microvascular architecture appears to be crucial to obtaining the greatest beneficial effect from residual spleen. In addition, quantities of regenerated spleen are usually far less than the original splenic mass, and preservation of any piece of spleen with an intact blood supply is preferable in terms of blood flow to a similar quantity of regenerated spleen.

Critical splenic mass

There is a concept of a critical splenic mass for protection against infection put forward by Van Wyck *et al.*[88]. They concluded that 30 per cent of the spleen was required for adequate antibody production. Cooney *et al.*[35] suggested that at least 50 per cent of the spleen was required to provide effective protection against experimental pneumococcal infections. Both these studies were in animals and required an intact splenic vascular supply. Corazza *et al.*[47] reported that a splenic volume of 30 cm^3 created by splenosis was the minimum required in humans to produce a restoration of splenic function sufficient to reduce the numbers of pitted erythrocytes, and that a splenic volume of 180 cm^3 should restore the blood picture to normal.

It is not known how much spleen is really required to prevent pneumococcal infection and the critical splenic mass is a theoretical concept rather than a practical recommendation.

Conclusions

Preservation of splenic tissue is indicated to prevent the later development of overwhelming pneumococcal infection. There is no doubt that splenic fragments can be placed in the peritoneal cavity where they will regenerate quite easily. These regenerated fragments appear histologically normal and function as spleen in terms of blood filtration, although it remains uncertain whether they are fully immunologically competent. The preferred technique of splenic autotransplantation is to use thin slices placed into omental pouches. This method carries the greatest chance of graft regeneration with tissue that most closely resembles normal spleen. In addition, in a few experimental studies grafts created in this manner have been demonstrated to be superior to grafts created by an alternative method. However, there is little evidence by which to state categorically that these regenerated splenic fragments are capable of protection of the host against pneumococcal infection. Case reports of severe infection in patients with regenerated spleen together with controversial results of animal experiments suggest that there is little overall beneficial effect. Splenic salvage with preservation of an intact splenic vascular supply to even a small amount of spleen is a more effective method of preserving splenic function than autotransplantation.

Limited reports of clinical experience with autotransplantation do not provide sufficient data from which to make judgements on its effectiveness, and splenic autotransplantation should therefore still be regarded as an experimental technique. Nevertheless, the procedure is quite simple and theoretically may confer possible benefits. It should not be abandoned until there is a greater understanding of the factors influencing the pathogenesis of pneumococcal infection in the asplenic state.

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Review

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Surgical management of primary hyperhidrosis

K. T. Moran and
M. P. Brady

University Department of Surgery, Regional Hospital and University College, Cork, Ireland

Correspondence to:
Professor M P. Brady

Primary hyperhidrosis, although lacking a precise definition and of unknown aetiology, disrupts professional and social life and may lead to emotional problems. A variety of treatment methods are used to control or reduce the profuse sweating which involves mainly the palms, soles and axillae. The simplest method, the application of topical agents, is usually attempted first for axillary and plantar sweating. Iontophoresis may provide relief especially in patients with plantar or palmar involvement. In severe cases operative intervention is necessary. Excision of sweat glands is successful in patients with axillary hyperhidrosis but the role of suction-assisted removal of axillary sweat glands remains to be determined. Sympathectomy remains the standard by which other treatments must be judged. For upper thoracic sympathectomy a variety of surgical approaches are used with satisfactory relief of hyperhidrosis. Complications related to the surgical approach, such as Horner's syndrome, brachial plexus injuries, pneumothorax and painful scars may occur, while following sympathectomy compensatory hyperhidrosis is usual and hyperhidrosis may recur. Plantar hyperhidrosis which may be exacerbated or ameliorated by upper thoracic sympathectomy and which fails to respond to non-operative intervention is relieved by lumbar sympathectomy.

Hyperhidrosis or sweating in amounts greater than that required for insensible loss or physiological needs may be primary (idiopathic) or secondary to other conditions such as hyperthyroidism, obesity, anxiety states and the menopause, or it may occur in paroxysms in association with phaeochromocytoma. Differentiation of normal sweating from hyperhidrosis is subjective and thus it lacks precise definition although attempts to measure normal rates of insensible loss from the skin have recorded values[1] of 8–15 $\mu g\ cm^{-2}\ min^{-1}$.

Primary hyperhidrosis

Primary hyperhidrosis usually appears in childhood and persists for life[2]. The sweat is secreted by eccrine glands innervated by cholinergic fibres from the sympathetic nervous system. These glands are located over the entire body but principally over the palms and soles and in the axillae. Sweating is precipitated by stimuli such as emotional excitement, heat and taste rather than exercise and it ceases completely during sleep[2,3]. Axillary hyperhidrosis is socially embarrassing, causing wetness, staining and rotting of clothing[4]. Patients with palmar involvement are reluctant to shake or hold hands and may become socially withdrawn. They are unable to grasp objects, papers become wet, ink runs and metals rust[4]. Plantar hyperhidrosis leads to bromhidrosis, blisters, infections and rotting of socks and shoes[4].

Management

The treatment of secondary hyperhidrosis which involves removal or control of the underlying cause will not be discussed here. Primary hyperhidrosis may be managed by a variety of techniques directed specifically at reducing the sweating to an acceptable level or abolishing it altogether. In this review the various treatment methods for primary hyperhidrosis are discussed. Non-operative approaches include local measures, application of topical agents such as aluminium chloride, glutaraldehyde and tannic acid, iontophoresis, systemic anticholinergic medication and psychotherapy. Operative treatment includes excision of axillary sweat glands, suction-assisted lipolysis and sympathectomy.

Local measures

Patients with plantar hyperhidrosis should apply an absorbent foot powder after bathing. Leather shoes and cotton or woollen socks should be worn, avoiding rubber and synthetic materials except for those activities that necessitate their use.

Topical agents

Aluminium chloride is the most widely used topical agent and may be adequate for some patients with axillary hyperhidrosis but its use in palmar and plantar hyperhidrosis has been less rewarding[4]. It may work by mechanically obstructing the eccrine sweat gland pore[5] or by causing atrophy of the secretory cells[6]. Varying success rates in the treatment of axillary hyperhidrosis have been reported (*Table 1*) Treatment is limited by the fact that half the patients who use aluminium chloride experience some degree of axillary irritation[7] but aluminium hexahydrate chloride in an alcohol base may cause less irritation. Tanning agents, glutaraldehyde and tannic acid are usually effective in the treatment of hyperhidrosis but are associated with brown staining that precludes their use in most instances[4].

Iontophoresis

This procedure, which coagulates eccrine sweat glands electrically, can be used to treat palmar and solar hyperhidrosis and, using a special electrode, axillary hyperhidrosis can also be treated[4,20,21]. The technique has been well described and

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Table 1 *Success rates with topical agents and surgical sympathectomy*

Treatment	Series	No. of patients	Successful outcome
Topical			
Aluminium chloride	Scholes *et al.*[7]	65	64
	Ellis and Scurr[8]	42	35
	Perdikis and Hansen[9]	50	48
	Jensen and Karlsmark[10]	38	12
Glutaraldehyde	Juhlin and Hansson[11]	25	25
Sympathectomy			
Endoscopic	Kux[12]	63	55
	Malone *et al.*[13]	17	17
	Byrne *et al.*[14]	112	101
Cervical	Bogokowsky *et al.*[2]	42	42
	Greenhalgh *et al*[15]	28	28
	Bass *et al.*[16]	133	126
	Adar *et al*[17]	100	100
Transaxillary	Ellis[18]	62	61
	Sternberg *et al.*[19]	70	66

widely used[20,21]. A direct current of 15–30 mA is supplied by a galvanic generator via electrodes. Initially, treatment sessions last for 20 min and treatments can be repeated from three to six times weekly until the desired results are obtained. Maintenance treatment can be performed as frequently as is necessary[22]. Treatments may be made more effective by the addition of anticholinergic agents such as poldine methylsulphate and glycopyrronium bromide[23,24]

Systemic anticholinergic agents

Primary hyperhidrosis can be effectively treated with systemic anticholinergic agents but unpleasant side-effects such as blurred vision, dry mouth and urinary retention preclude their use except for very brief periods

Psychotherapy

Patients with hyperhidrosis often have psychological disturbances[2] and have frequently been treated with tranquillizers before referral for surgical treatment. Psychotherapy or biofeedback has been used with limited success by some authors[25]. This is not surprising because there is no evidence that hyperhidrosis is primarily a psychiatric disorder and it would appear that psychological disturbances are caused by the difficulties the patient experiences in establishing social and professional activities[2–4]. Greenhalgh *et al.*[15] found that five of their 28 patients were referred for surgical treatment by psychiatrists because their emotional instability, rather than being the primary cause, seemed to be aggravated by the disability.

Interruption of sympathetic innervation of the upper limb and axilla

The inferior cervical ganglion and the first thoracic ganglion fuse to form the stellate ganglion. Sympathetic outflow to the upper extremities is usually from T2 to T9 but in 10 per cent of cases fibres from T1 and thus the stellate ganglion contribute to arm innervation[26]. There may also be a direct connection between the second and third thoracic ganglia and the brachial plexus, the nerve of Kuntz[27]. The choice of method of sympathetic interruption is difficult because the anatomy of the sympathetic outflow to the upper extremity is sometimes misrepresented by anatomists[28] and often varies from side to side in the same individual[29]. Roos believes that the optimal surgical sympathectomy for the upper extremity may be achieved by dividing the sympathetic chain immediately below the stellate ganglion and just above the T3 ganglion, removing this part of the chain and then dividing the nerve of Kuntz lateral to the chain as well as the gray rami that pass from the stellate ganglion to the brachial plexus[30]. Resecting the fourth and fifth ganglia will effectively denervate the axilla[30].

Excision of axillary sweat glands

In upper limb hyperhidrosis the axillae alone are affected in some 37 per cent of cases, the hands and axillae in 43 per cent and the hands in 20 per cent[3]. Axillary hyperhidrosis in patients who are unresponsive to medical therapy can be effectively treated by excision of axillary sweat glands[31–33]. The area of greatest concentration of eccrine sweat glands corresponds to the hairy portion of the axilla[34] and can be accurately identified by the bluish purple discoloration produced when starch iodine is exposed to sweat. The simplest method described by Hurley and Shelley in 1963 involves the excision of this area[35]. A transverse incision parallel with the normal skin creases is used to minimize the possibility of restriction of movement after operation. These authors later modified their technique for patients with severe hyperhidrosis[36]. In these patients they advocated additional excisions peripheral to the central excision with undermining and resection of the sweat glands around each excision. Breach, seeking to avoid skin excisions which might lead to unsatisfactory scarring, made three transverse incisions in the axilla and removed all subcutaneous tissue from the bipedicle flaps which were developed[37]. In that study 23 of 25 patients had satisfactory results at 1 year. Axillary scar contracture may be avoided by incorporating a Z-plasty in the closure[8,9]. As an alternative Stenquist[31] used bat-shaped axillary excisions in 14 consecutive patients and reported excellent results in 12 of them. When axillary and palmar hyperhidrosis are associated the upper thoracic sympathectomy is extended to include the fourth or even fifth ganglion[15,39] but in a percentage of cases, reported to be as high as 40 per cent in one study, this fails to cure axillary hyperhidrosis[39]. In these patients upper thoracic sympathectomy may be combined with excision of sweat glands.

Suction-assisted lipolysis

Suction-assisted lipolysis has been accepted as a standard surgical technique for a number of years[40], but the concept of suctioning the subdermal tissue in the axilla in an attempt to remove sweat glands is new, although it has been successfully used[41,42]. The distribution of sweat glands in the axilla deep to the dermis and superficial to the axillary fat pad and fascia suggests that they might be amenable to this technique. The operation is performed as an outpatient procedure under general or local anaesthesia. Suction is carried out through a 1 cm incision in the anterior axillary fold and the entire surface of the dermis is 'vacuumed' in all directions with 15–20 strokes using a 5 or 7 mm diameter cannula. The area treated includes the area of maximum hair growth and 5–6 cm beyond.

Surgical approaches for upper thoracic sympathectomy

A variety of surgical approaches have been used for upper thoracic sympathectomy. In 1933, White *et al.* developed a two-stage procedure involving a dorsal paravertebral incision for access to the sympathetic chain[43]. The cervical approach was introduced in 1935 as a single procedure[44]. Kux advocated an endoscopic technique in 1954 to avoid major surgical dissections and their ensuing morbidity[45]. The axillary approach of Atkins (1954) was designed to provide a simple anatomical approach to the sympathetic chain[46]. The transthoracic approach of Palumbo and Lulu (1966), although providing the best exposure, involved the morbidity and even mortality of a thoracotomy[47]. The dorsal midline approach of

Cloward (1969) allows access to the sympathetic chain on both sides[48]. Roos (1971) modified the Atkins technique and approached the sympathetic chain extrapleurally having resected the first rib[49] All these methods have intrinsic advantages and disadvantages but only the endoscopic, cervical and axillary methods are used widely.

Endoscopic thoracic sympathectomy

The technique is described as a safe effective treatment applicable to patients with both axillary and palmar hyperhidrosis[12]. A preoperative chest radiograph is essential to exclude pulmonary pathology. The patients are anaesthetized using a double-lumen endotracheal tube. Through a small incision in the third intercostal space in the anterior axillary line, a needle is introduced and a pneumothorax is produced by insufflating 1·5 litres of carbon dioxide. A laparoscope is then inserted and the sympathetic chain is visualized running vertically over the necks of the ribs Diathermy forceps are inserted through a separate stab incision in the fourth intercostal space The chain is coagulated from the second ganglion to the fifth or sixth ganglion. Following coagulation the pneumothorax is released and the lung is inflated under direct vision. The same procedure is repeated on the other side. Varying success rates have been reported (*Table 1*) and although this method has not gained widespread use or acceptance it has the advantage that patients are out of hospital in 3 days and can return to work within the week[13].

Cervical approach

We have used this approach in more than 100 patients It requires a meticulous surgical technique because of the important anatomical structures encountered including the brachial plexus, phrenic nerve, apical pleura and stellate ganglion. We consider it worthwhile to describe the operation in detail

The incision, placed one finger's breadth above the clavicle, is 6–7 cm long and should be centred over the lateral edge of the clavicular head of the sternomastoid. The subcutaneous fat and platysma are divided by cutting diathermy disregarding any cutaneous branches of the supraclavicular nerves. The lateral fibres of the sternomastoid are divided in a similar fashion. The outline of the scalenus anterior is palpated through the scalene fat pad and forms the centre of the subsequent dissection The fat pad is defined laterally used dissecting scissors. The fascia overlying the scalenus anterior is divided. A London Hospital retractor is then used to retract the fat pad and fascia medially taking the phrenic nerve with it. The scalenus anterior, the deep portion of which is tendinous, is divided serriatim by picking up the muscle in small pieces and dividing with scissors. The Gothic (as opposed to Roman) arch of the subclavian artery is now fully exposed The suprapleural membrane, apical pleura and apex of the lung are dissected from the first rib using the broad sweep of the operator's thumb. (The index finger or a small dissecting swab offers too narrow a focus and will tear the pleura.) A malleable copper retractor is used to keep the apex of the lung out of the operative field and a single Langenbach retractor retracts the subclavian artery upwards and medially. (Use of two retractors will cause a parallelogram of forces and injure the artery)

A spotlight is focused into the operative field and the upper thoracic chain is palpated by the index finger as it crosses the neck of the first rib descending along the side of the first thoracic vertebra. This is dissected free and a blunt hook is used to elevate the chain between the stellate and second thoracic ganglia. A metal clip is applied below the stellate ganglion which resembles a snowman standing on its head. The blunt hook is now replaced with a long fine artery forceps. The chain is divided below the clip and dissected downwards taking the second thoracic ganglion and placing clips on the white and grey rami entering and leaving the ganglion because small blood vessels may accompany these nerves. A metal clip is applied to the upper portion of the third ganglion and the chain is divided above this point All specimens are sent for histological examination. The incision is then closed following expansion of the lung in a pool of saline to exclude pleural injury. Small tears in the apical pleura can usually be treated by closure of the surgical wound over a rubber drain which is extracted after skin closure. The platysma and subcutaneous fat are closed with a continuous 3/0 chromic catgut stitch Adhesive paper strips are used to approximate the skin

The advantages of this approach are that bilateral procedures may be performed and there is less postoperative pain. In addition, this is the most suitable approach for children and in one study it was used successfully to treat children as young as 6 years of age[50]. The major disadvantage of this approach is that it is difficult to reach the fourth thoracic ganglion which must be destroyed to control axillary hyperhidrosis Satisfactory results have been reported (*Table 1*)

Transaxillary approach via third interspace

This is a transpleural approach and is contraindicated if there is evidence of adhesions between the visceral and parietal pleura. The incision follows the line of the third rib downwards and forwards from the posterior to the anterior axillary fold The pectoral muscles and breast are retracted forwards and the latissimus dorsi and subscapularis muscles backwards The long thoracic nerve is protected under the posterior retractor The third rib is exposed by incising the overlying fibrofatty tissue of the axilla and removing the serratus anterior from its attachment to this bone The periosteum of the rib is incised with a diathermy knife and separated from the upper surface and the back of the rib The pleura is now opened, a rib spreader inserted and the lung retracted downwards. The sympathetic chain can easily be seen beneath the pleura as it lies on the heads and necks of the ribs. The parietal pleura is opened to expose the chain and a sympathectomy is performed Transaxillary sympathectomy, although regarded by some authors as the standard operative treatment for upper limb hyperhidrosis, has disadvantages[18] It may be safest to operate on one side at a time so patients require two hospital admissions. Advocates of transaxillary sympathectomy reserve the operation for patients with both axillary and hand sweating, employing more local measures for axillary sweating alone[18,19]

Plantar hyperhidrosis

Excessive sweating of the feet usually accompanies upper limb hyperhydrosis[3,4] Although plantar hyperhidrosis may be equally distressing, when offered a choice of area to be treated. the majority of patients opt for treatment of the upper limb[3] Plantar hyperhidrosis may be exacerbated following upper thoracic sympathectomy[2]. In one study, all 42 patients operated on suffered from plantar hyperhidrosis and, although the condition subsided temporarily in the majority, it recurred in all cases at various times during follow-up[2] Conversely other authors have reported an improvement in plantar sweating following upper thoracic sympathectomy[4,48]. Cloward described the appearance of dryness in the lower limbs in 22 per cent of cases after upper thoracic sympathectomy and he postulated that this phenomenon is the result of abnormal cortical representation of sudomotor function[48]. Plantar hyperhidrosis may be more amenable to non-operative intervention than upper limb hyperhidrosis. Local methods are useful and tanning agents which cause unacceptable staining elsewhere can be used on the feet[4,11]. Iontophoresis has also been used successfully[20,21] In severe cases lumbar sympathectomy relieves symptoms[4,51].

Lumbar sympathectomy

The lumbar sympathetic chain is exposed using an anterior extraperitoneal approach. The umbilicus is situated approximately level with the middle of the lumbar chain An oblique incision beginning near the tip of the 12th rib is extended close to the umbilicus. After the skin is incised the subcutaneous fat and external oblique aponeurosis is divided by cutting diathermy. The internal oblique and transversus muscles are split along the line of their fibres Before splitting the internal oblique, a 2 cm transverse incision is made in the lateral edge of the rectus sheath and the rectus muscle is elevated using a London Hospital retractor allowing the peritoneum to fall away. The peritoneum is stripped from the lateral, anterior and finally the posterior abdominal wall to expose the psoas muscle. As dissection proceeds the ureter is retracted forward with the peritoneum, and the genitofemoral nerve is identified on the anterior border of the psoas. The sympathetic chain lies medial to the psoas muscle on the vertebral column, covered on the right side by the inferior vena cava while on the left side it lies close to the aorta. It is most readily identified by palpation of its ganglia although it may be confused with retroperitoneal lymph nodes, the genitofemoral nerve or the tendon on the psoas muscle. Removal of ganglia L2–L4 denervates the limb from the lower third of the leg distally, effectively relieving symptoms[52]. Bilateral removal of the first lumbar ganglion may interfere with ejaculation[52]. In our experience this technique enables the procedure to be done in less than 10 min for each side. As an alternative to open lumbar sympathectomy, the sympathetic ganglia can be injected with up to 5 ml of 6 per cent phenol in water for a semipermanent denervation[53].

Discussion

The cause of hyperhidrosis is unknown but the condition can have devastating consequences for work and social activities[2–4]. The initial treatment chosen should be the safest, simplest and least expensive method that could reasonably be expected to prove beneficial[4]. Excellent results have been reported in some studies using topical agents but because hyperhidrosis lacks a precise definition it is difficult to compare these patients with those in other series who had operative intervention[2,7,8]. Although another non-operative method, iontophoresis, has been widely used information on success and failure rates and long-term follow-up is not available[20,23,24]. In general non-operative approaches have proved disappointing.

It is clear that surgery is the treatment of choice in severe cases[2,3,16–18], yet some authors have noted a reluctance by physicians to refer patients, many patients being seen after years of conservative management that left both patients and physician frustrated[2,15]. As the operation is intended to improve the quality of life and is not essential for longevity the patient should be aware of the potential complications and sequelae. Indeed, one group reported that they use a detailed consent form that serves as a screening test to determine which patients are sufficiently motivated to undergo surgery[17]. Resection of axillary sweat glands alone can effectively treat upper limb primary hyperhidrosis in almost 40 per cent of patients[3,34–36]. Advances in surgical technique should allow primary healing with minimal morbidity from infection, skin necrosis or wound contracture[31,38,39]. Suction-assisted removal of axillary sweat glands theoretically has potential but as yet only anecdotal reports testify to its value[41,42].

Sympathectomy remains the gold standard by which other treatments must be judged but it is not without problems, both with regard to the surgical approach and the consequences of sympathectomy. The end results, cessation of excessive sweating, are satisfactory whatever the approach. However, the variety of surgical approaches used indicates that no ideal method of sympathectomy exists. The endoscopic technique involves a learning curve even for experienced surgeons but when this method is mastered, morbidity is diminished[12–14]. The bilateral cervical approach useful in both children and adults is technically the most difficult and is associated with the highest incidence of complications including Horner's syndrome, brachial plexus injuries and pneumothorax[2,15–17]. The transaxillary approach, although providing better exposure, is associated with more severe postoperative pain, a longer convalescence period and a significant long-term incidence of neuralgia and painful scars[18,19,54]. In addition, two operations are usually required. Other approaches are rarely used because of technical difficulties, operative morbidity and even mortality[43,47–49].

Horner's syndrome is related to the approach used For cervical sympathectomy the reported incidence varies from zero[2] to 40 per cent[17]. Using this approach Greenhalgh[15] reported an incidence of 4 per cent while only one of Bass's 133 patients had a 'severe' Horner's syndrome on follow-up although 26 patients had minor degrees of this syndrome[16]. These wide variations indicate that, in addition to the surgical approach, other factors such as the technical expertise and experience of the surgeon must play a role. Using the transaxillary route Horner's syndrome was not observed in two series[18,19], while other studies using the endoscopic approach had similar findings[12–14]. Using a dorsal midline approach in the largest series in the literature (457 patients) with hyperhidrosis treated by sympathectomy, there was no incidence of Horner's syndrome[55].

Some degree of compensatory hyperhidrosis appears in almost all patients irrespective of the surgical approach used[2,12,15,16,18,19,55]. Following upper thoracic sympathectomy for palmar sweating, axillary hyperhidrosis may occur if the axilla is not denervated[15]. Usually the chest, abdomen and thighs are involved but plantar hyperhidrosis may also ensue[12,15,16,54–56]. Usually these symptoms abate over time. Extensive sympathectomy distal to the fourth thoracic ganglion seems to be associated with a more severe compensatory hyperhidrosis[12].

Gustatory phenomena following sympathectomy have been described in less than 5 per cent of patients[12,31,55,56]. It has been postulated that they represent an expression of aberrant regeneration or collateral sprouting of preganglionic fibres, making abnormal synapses in the superior cervical ganglion[57]. Gustatory sweating can be prevented or alleviated by extending sympathectomy to the lower one-third of the stellate ganglion[12].

Recurrent sweating may occur after apparently successful upper dorsal sympathectomy[2,15,16,44,54]. Some degree of sweating returns in almost all patients and this is preferable to a completely dry skin. The mechanism of recurrence is unclear but there are a number of possible explanations. Haxton has shown nerve regeneration in histological specimens obtained from a second operation[58,59]. In addition, anatomical variations involving the stellate ganglion and sympathetic chain have been noted[60].

It is clear from the literature that the vast majority of patients who undergo sympathectomy for hyperhidrosis are pleased with the result. Careful selection of patients and meticulous surgical technique will minimize morbidity but there will always be an incidence of unpleasant sequelae irrespective of the technique used. In the words of Telford, one of the pioneers of sympathectomy, quoted in Adson *et al.*[44], 'I do not think that any operator who has had sufficient experience of sympathectomy and followed up his patients for some years can regard the outcome of his work as entirely satisfactory'[44]

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Intra-arterial thrombolytic therapy in the management of acute and chronic limb ischaemia

H. Barr, M. J. R. Lancashire, E. P. H. Torrie* and R. B. Galland

*Departments of Surgery and *Radiology, Royal Berkshire Hospital, London Road, Reading, Berkshire RG1 5AN, UK*

Correspondence to:
Mr R B. Galland

A group of 54 patients with acute or chronic limb ischaemia were initially treated with low dose intra-arterial thrombolytic therapy using streptokinase (10 000 units h^{-1}) or plasminogen activator (0·5 mg h^{-1}). Complete thrombolysis was obtained in 90 per cent of patients with symptoms of less than 1 week duration, and in 50 per cent with symptoms of greater than 1 week ($P<0{\cdot}05$)*. Successful lysis in 36 patients was followed by successful bypass surgery in seven, percutaneous angioplasty in 13, no further treatment in 13, repeat thrombolysis in two and amputation in one. Failed therapy was associated with major amputation in 40 per cent. One patient died of haemorrhage and another of stroke as a direct result of thrombolytic treatment. The most common complication was haematoma at the site of cannulation of the vessel. Intra-arterial thrombolytic therapy can be very useful for the management of acute and chronic limb ischaemia, but complications do occur and patients should be carefully selected.*

Acute non-traumatic lower limb ischaemia is usually caused by arterial embolism or thrombosis of atherosclerotic vessels, and is associated with death in approximately 25 per cent and major amputation in 20–40 per cent of patients[1]. The management of embolism is usually by balloon embolectomy[2] which provides the best chance of preserving life and limb function, although type 1 emboli (embolism of a large vessel) are associated with a 63 per cent incidence of death or disability[3]. This is partly because many patients after embolectomy are left with residual arterial thrombus[4,5]. It can be particularly difficult to clear all of the calf vessels, because the anatomical configuration means that embolectomy catheters inserted proximally enter the peroneal artery repeatedly rather than the anterior or posterior tibial vessels[6].

Although the presence of collateral vessels associated with purely thrombotic occlusion of arteries may limit the initial severity of the ischaemic episode, the management is often more complex and usually requires urgent reconstructive surgery. However, the results of operation are often poor[7], due to many factors, such as failure to identify adequately the underlying problem, and inadequate treatment of secondary thrombosis producing poor distal outflow[8]. The prospect of selective clot lysis instead of, or preceding, reconstruction is attractive.

The discovery, at the end of the 19th century, that under certain circumstances established clot could be lysed and dispersed, led to investigation of therapeutic thrombolysis[9]. Although systemic fibrinolysis in the treatment of arterial occlusion produced recanalization[10,11], the introduction of catheter directed low-dose infusion of streptokinase proved more effective[12]. The precise role and efficacy of this technique remain controversial[13], and it is not widely used in this country despite some encouraging reports[14,15].

In this investigation intra-arterial thrombolysis was used in the management of acute thromboembolic arterial disease in patients with critically ischaemic but viable limbs. In addition, patients with subacute and chronic limb ischaemia due to thrombotic occlusion, with symptoms severe enough to require invasive treatment but unsuitable for immediate angioplasty or reconstructive surgery, were also treated.

Patients and methods

Patients

A group of 54 patients with 56 ischaemic limbs were treated between November 1988 and January 1990. In addition two patients were treated on two separate occasions for reocclusion of the same limb. The decision to offer the patient intra-arterial thrombolytic therapy was generally taken following clinical assessment and an intravenous digital subtraction angiogram (IVDSA). In three patients, with a palpable femoral pulse but acute distal ischaemia, a formal ipsilateral femoral arteriogram was the initial radiological investigation. A total of 37 men and 17 women (median age 69 years, range 44–71 years) were considered suitable for treatment The aetiology of the ischaemic limb is shown in *Figure 1*. Patients with a history of a cerebrovascular accident within 6 months, dyspepsia, peptic ulceration, gastrointestinal haemorrhage, recent operation or haemorrhagic problems were excluded.

Of the patients, 37 presented with rest pain and a critically ischaemic leg[16]; 24 presented within 1 week of the acute episode, ten within 4 weeks and the remainder up to 10 weeks afterwards; five of these patients had ulceration and digital gangrene. One patient presented on two separate occasions with acute thrombosis of separate popliteal aneurysms, and one patient had bilateral ischaemic limbs. One patient presented with a brachial embolus causing an ischaemic but viable upper limb Five patients presented following acute deterioration of an already compromised leg with severe incapacitating intermittent claudication Two diabetic patients presented with ulceration and gangrene as the predominant symptom. Following superficial femoral angioplasty four patients had an embolus at the popliteal trifurcation. All three calf vessels were occluded in three patients and the posterior tibial artery alone in one. The other three occlusions following angioplasty were due to superficial femoral thrombosis at the site of the treated stenosis

Before starting intra-arterial thrombolysis a femoral arteriogram was performed. Two patients with a blocked Dacron® (E I du Pont de Nemours and Company) aortic bifurcation graft required axillary artery punctures. If the formal arteriogram confirmed the nature of the occlusion seen on the DSA, a size 5–7 French gauge infusion catheter was inserted into the artery following passage of a guide wire. The tip of the catheter was placed in the clot or just proximal to the occlusion.

Thrombolytic regimen

Streptokinase (Kabikinase®, KabiVitrum, Uxbridge, UK) was generally used and was infused at a rate of 10 000 units h^{-1} with heparin 500 units h^{-1}. The concentration of the infusate was adjusted to allow volume infusion of 2 ml h^{-1}. In three patients recombinant human tissue-type plasminogen activator (rtPA, Actilyse, Boehringer Ingelheim) was infused at a rate of 0·5 mg h^{-1} with 500 units of heparin h^{-1}. One patient had been treated 6 weeks previously with streptokinase for thrombosis of a popliteal aneurysm, which was subsequently successfully bypassed The IVDSA had shown a contralateral popliteal aneurysm but this thrombosed before it could

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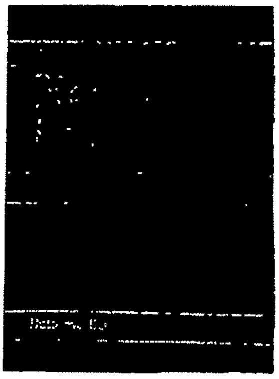

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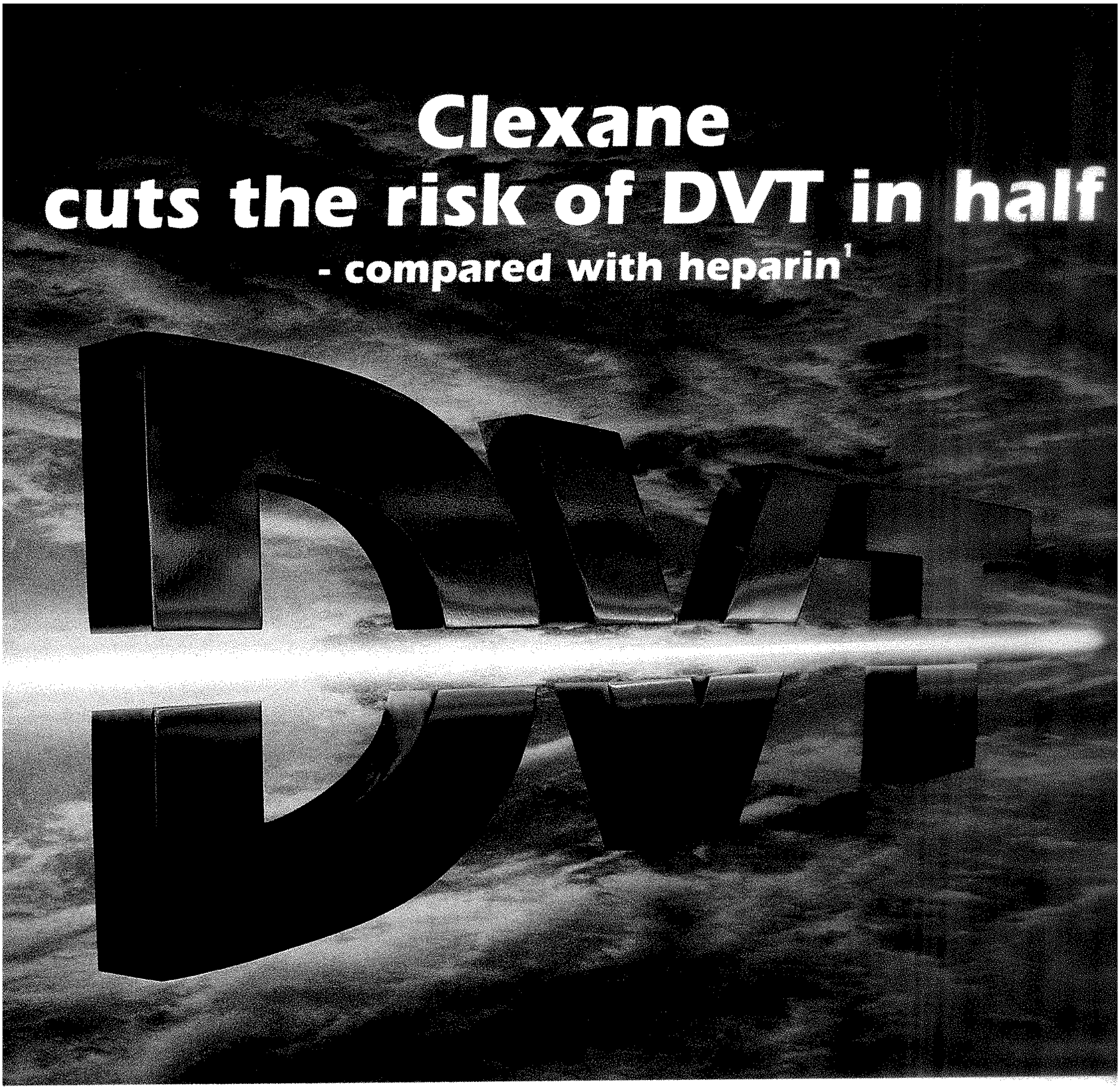

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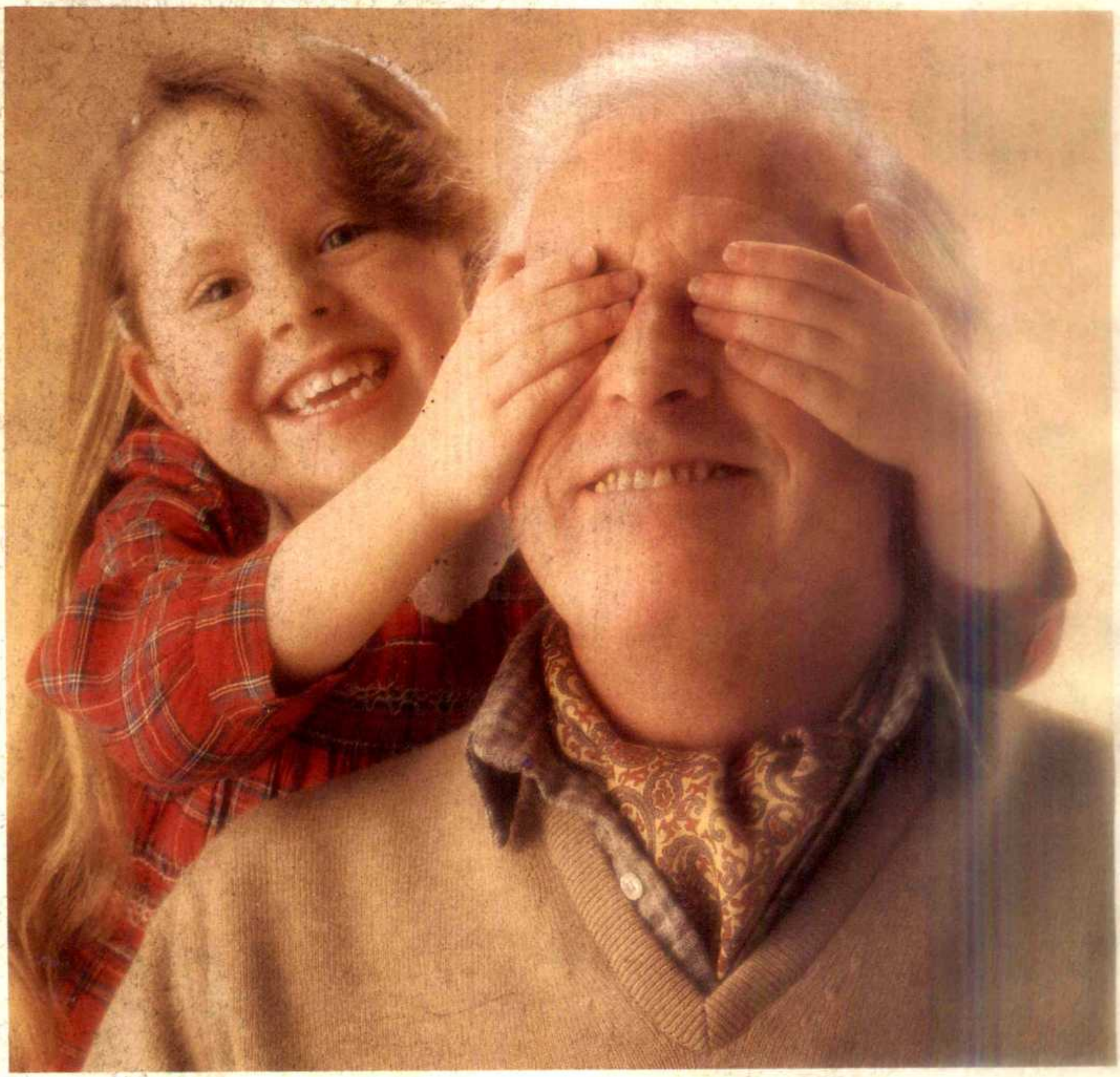
Guess which prostate cancer treatment most patients would choose.



In a recent study[1], 57 prostate cancer patients were invited to participate in choosing their treatment. All were informed that the two treatments available, sub-capsular orchidectomy or 'Zoladex', were similar in efficacy and side effects. 49 of the patients (86%) opted for 'Zoladex'.

A recent trial[2] has established the equivalence of 'Zoladex' to orchidectomy.

Zoladex

goserelin

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Consult data sheet before prescribing. Use: Prostate cancer suitable for hormonal manipulation. **Presentation:** A sterile depot containing goserelin 3.6mg. **Dosage and administration:** One depot injected subcutaneously into the anteropr abdominal wall every 28 days. **Precautions:** Patients at particular risk of developing ureteric obstruction or spinal cord compression. Consider initial use of an anti-androgen at the start of therapy. An increase in benign pituitary tumours has been observed in male rats following long-term repeated dosing. This finding is similar to that previously noted in this species following surgical castration (relevance to man not established). **Side effects:** Hot flushes, decrease in libido and occasional breast swelling and tenderness. Skin rashes (generally mild). Occasional mild bruising at injection site. Initial transient increase in serum testosterone may cause temporary increase in bone pain. **Product Licence number:** 29/0198. **Basic NHS cost:** £125.40 per depot. 'Zoladex' is a trademark. Further information is available from: ICI Pharmaceuticals (UK), Southbank, Alderley Park, Macclesfield, Cheshire SK10 4TF.

Reference: 1. Luriglmayr G, Girsch E. In Chisholm G D ed. *'Zoladex' – a new treatment for prostatic cancer. International* Congress and *Symposium Series*. 125. London: RSM Series, 1987: 47-51.
2. Peeling W B. Proceedings of the 'Zoladex' Scientific Launch Meeting 1987.

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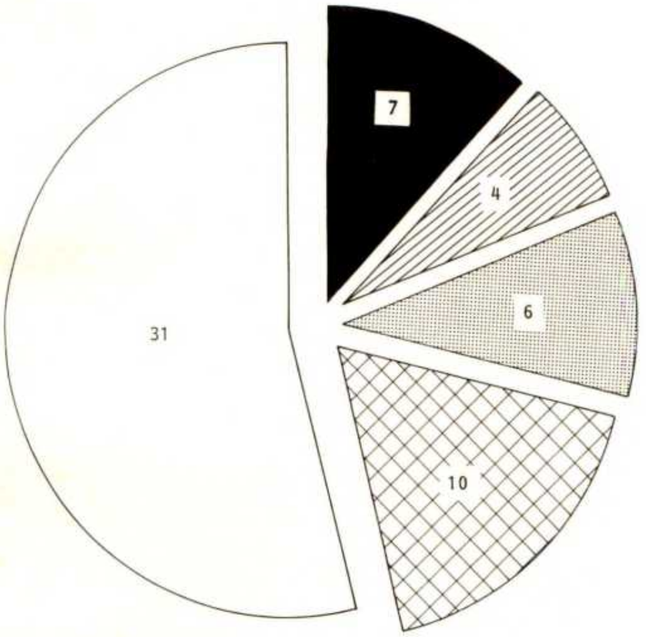

Figure 1 *Pie chart to show the aetiology of the ischaemia in 58 limbs.* ■, *Postangioplasty occlusion;* ▨, *acute embolus;* ⊡, *popliteal aneurysm thrombosis;* ⊠, *graft thrombosis;* □, *femoral/popliteal thrombosis*

be dealt with. Lysis and bypass of this aneurysm was also successful. The two other patients reoccluded their superficial femoral artery 10 days and 6 weeks after initial successful lysis.

Following catheter insertion, the patient was returned to the ward and had repeat arteriography in the radiology department every 6–12 h depending on the progress of lysis. The position of the catheter was adjusted to ensure that its tip was placed in the clot. If there was difficulty in placing or maintaining the catheter in the clot, or there was no progress in lysis after 24–48 h, therapy was abandoned and other options considered. Treatment was stopped immediately if significant complications developed. Effective lysis was confirmed by arteriography. If an underlying lesion was identified, further treatment with immediate percutaneous balloon angioplasty or bypass was carried out. On withdrawal of the streptokinase infusion catheter, 1000 units of heparin were injected, and firm local pressure was applied to the entry site.

Results

Two patients presented with myocardial ischaemia and subsequently developed ischaemic legs due to an embolus. They died of cardiogenic shock unrelated to the treatment before its completion. One other patient died shortly after starting treatment. The results of treatment are analysed for 53 limbs of 51 patients.

The median duration of treatment for all patients was 47 h. Those who had partial or no lysis were treated for 43 h and those with complete lysis for 52 h. Overall, lysis occurred in 36 patients (38 limbs). Complete lysis was significantly more likely if treatment occurred within 1 week of the onset of symptoms (*Figure 2*). Nevertheless, lysis failed in three of 31 patients with symptoms that were present for less than 1 week. In two patients the occlusion was an embolus to the popliteal trifurcation following superficial femoral angioplasty. One patient had a formal embolectomy after unsuccessful thrombolysis. The embolus was found to be a detached atheromatous plaque rather than a clot. The second patient had partial lysis of a popliteal embolus but refused surgical exploration despite only partial resolution of her symptoms. She subsequently improved spontaneously over a period of days. The third patient had failed lysis of an acutely thrombosed femoropopliteal Gore-Tex® (W. L. Gore and Associates Incorporated) graft. It was extremely difficult to position the thrombolysis catheter into the graft and most of the infusion entered the profunda femoris artery. Treatment was therefore abandoned after 24 h and successful revisional bypass surgery performed.

As shown in *Table 1*, 13 patients required no further treatment after successful lysis (median follow-up 6·5 months). One patient had successful lysis of a brachial embolus. The ankle/brachial pressure index before and after thrombolysis in the other 12 patients (13 legs) is shown in *Figure 3*. Two patients required retreatment following reocclusion, both of whom achieved successful repeat lysis with rtPA and remain improved 1 and 3 months after retreatment.

Further treatment following successful lysis was needed in 21 patients. Percutaneous angioplasty of an underlying stenosis was required by 13 patients. Angioplasty was usually performed as soon as complete thrombolysis was confirmed. In two patients despite radiological improvement there was no improvement in the pressure index. Both patients felt symptomatically better and no further treatment was required.

One patient required femoropopliteal bypass surgery when angioplasty was unsuccessful and one patient required surgery for the revision of the stenotic lower end of a thrombosed femoropopliteal bypass graft. In one patient, there was complete clearance of an acutely thrombosed femorodistal graft. However, the run-off did not open up and despite fasciotomy and exploration a below knee amputation was performed. All five patients with thrombosis of six popliteal aneurysms had successful thrombolysis and were all subsequently treated by a bypass graft.

The outcome for the patients who had failed to achieve complete thrombolysis is shown in *Table 2*.

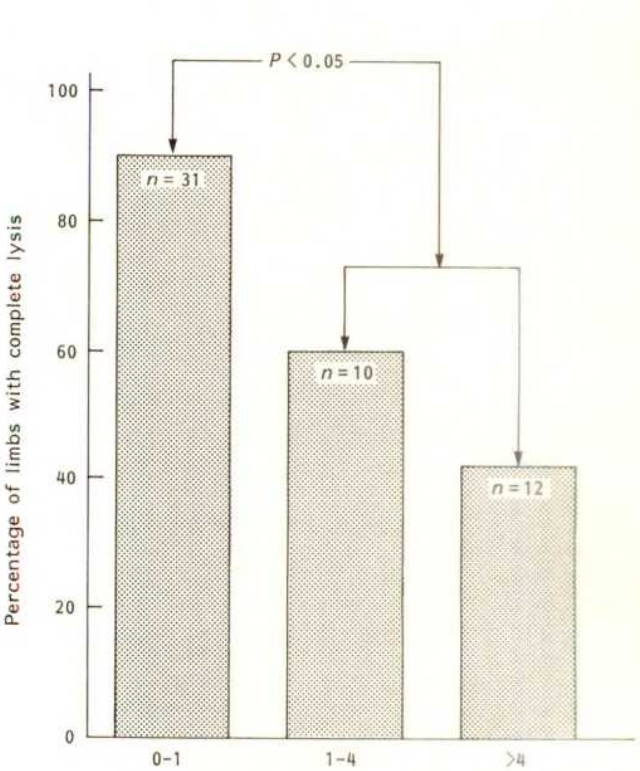

Figure 2 *Percentage of limbs achieving complete lysis compared with duration of symptoms* (χ^2 *test*)

Table 1 *Outcome after successful complete thrombolysis in 36 patients (38 limbs)*

	No. of patients	No. of limbs
No further treatment	13	14
Repeat thrombolysis	2	2
Percutaneous angioplasty	13	13
Successful bypass surgery	7	8
Below knee amputation	1	1

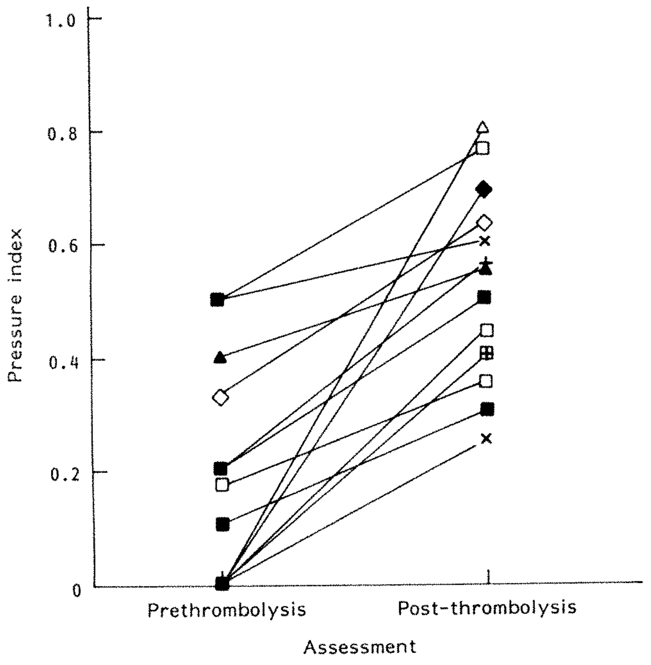

Figure 3 *The resting ankle/brachial pressure index before and after complete thrombolysis in 12 patients (13 lower limbs) who required no further treatment*

Table 2 *Outcome after failed thrombolysis in 15 patients*

	No. of patients
Spontaneous improvement (after partial lysis)	2
Spontaneous improvement (after no lysis)	1
Successful bypass surgery	2
Above knee amputation	5*
Below knee amputation	1*
Successful delayed embolectomy	1
Chemical sympathectomy	2
Failed thrombolysis but death from cerebrovascular accident	1

* These patients had chronic ischaemia with no run-off, producing critically ischaemic limbs

Table 3 *Complications*

Complications of infusion of thrombolytic agent	
Fatal	
Haemorrhage	1
Cerebrovascular accident	1
Non-fatal	
Gastrointestinal haemorrhage	3 (conservative treatment)
Septicaemia	1
Groin haematoma	7
Axillary haematoma	1
Procedural complications	
Catheter breakage	1
Guide wire break	1
Complications related to patient factors	
Death from concomitant disease during procedure (myocardial insufficiency)	2

Complications (Table 3)

Two patients died as a result of treatment. A 76-year-old woman with severe myocardial disease developed an acutely ischaemic limb following a thrombotic occlusion of the superficial femoral artery. This was successfully treated by streptokinase infusion through a catheter placed in the ipsilateral femoral artery. The underlying superficial femoral artery stenoses were dilated with balloon angioplasty. She collapsed and died 12 h later, before surgical exploration. At post-mortem a large retroperitoneal haematoma was identified in association with the iliofemoral artery puncture site, which was above the inguinal ligament. The other fatality was a 78-year-old man with an acutely ischaemic limb again associated with a thrombotic occlusion of the superficial femoral artery. He had had a fainting attack 2 weeks before treatment. There was no evidence of a neurological deficit and before thrombolysis a computerized tomographic scan failed to demonstrate any intracranial abnormality. Approximately 6 h after the start of treatment his neurological state deteriorated and a computerized tomographic scan demonstrated an intracranial haematoma.

Haematoma occurred in eight patients at the site of arterial puncture. None required exploration or became infected. Ipsilateral groin puncture was performed in 38 limbs and was associated with haematoma in seven patients, 14 patients had contralateral groin puncture without haematoma formation.

Discussion

In this series intra-arterial thrombolysis was successful in 90 per cent of patients if treatment was started within 1 week of the onset of symptoms. The failures in this group were because the embolus was atheromatous or there was inadequate placement of the catheter. It is interesting to note that even if the symptoms were present for more than 4 weeks, lysis was achieved in 40 per cent of patients. One patient in this series with an occluded popliteal aneurysm, who developed symptoms 3 years before treatment, obtained successful lysis. Nevertheless, these data demonstrate that intra-arterial thrombolysis should be used as early as possible. Others have also shown the importance of early treatment[17]. Although some authors have used thrombolysis in severely ischaemic limbs (loss of sensation and paralysis)[14], the technique in the presence of neurological signs is not used in this centre. Revascularization of severely ischaemic limbs with streptokinase infusion has been shown to be associated with a high rate of renal complications[18], and thrombolysis is not now generally recommended in such a situation[15]. In a large series Hess *et al.* demonstrated that embolic occlusions had to be treated earlier than thrombotic ones since organization of an embolus in a normal artery seemed to occur more rapidly than that of a thrombosis in an atherosclerotic artery[19].

In order to obtain prolonged patency most patients will require a further procedure[14,15,20]. Thrombolysis should simply be regarded as the initial management in many patients. In this series the invariable practice was to treat any arterial lesion as soon as possible after successful lysis. Approximately 55 per cent of patients required subsequent angioplasty, or bypass surgery. The patients who did not need further treatment were those who developed occlusion after angioplasty, those with acute emboli, and one patient with a graft occlusion in whom an underlying abnormality could not be demonstrated radiologically.

The usual dose of intra-arterial streptokinase is 5000–10 000 units h^{-1}, there being little apparent difference between the higher or lower dose regimen[21]. Precise examination of the factors that produce 'experience' with the technique is difficult. Analysis of the pattern of practice in the United States failed to demonstrate a significant correlation between results and experience, although in general, success was greatest in centres with the largest experience[22]. It is notable that the one centre with the largest experience had an 80 per cent success rate with intra-arterial thrombolysis. The experience in this centre is that there is a learning curve with improved patient selection in the latter part of the series. These observations may have important implications for the interpretation of data from small series, which have been dismissive of the usefulness of intra-arterial thrombolysis[13] and which have suggested it is not cost-effective[23].

Two patients died as a direct consequence of thrombolytic therapy, from local and intracerebral haemorrhage. Previous reports have not demonstrated that continuous haematological monitoring can predict haemorrhagic complications or indeed lysis[24,25]. Recently, monitoring the plasma fibrinogen has been suggested as a method of predicting incipient haemorrhage[21]. It was not the practice here to perform routine haematological assessment, the patients being managed purely on clinical grounds. The most signficant determinant of local bleeding complications has been shown to be related to the position of the entry site, axillary artery catheters and catheters placed above the inguinal ligament in the ipsilateral iliofemoral segment producing most problems[26]. In the present series local haematoma was always associated with ipsilateral supra-inguinal puncture, although too few contralateral punctures were performed to allow meaningful comparison. Major haemorrhage (i.e. that requiring transfusion of blood or clotting factors, or being associated with hypotension) occurs in approximately 5 per cent of patients undergoing intra-arterial thrombolysis. Similarly minor haemorrhage, mainly local haematoma, occurs in 15 per cent of patients[21] The overall risk of haemorrhagic stroke is 1 per cent[21,22] and it has been suggested that careful assessment of patient risk factors could reduce this[22]. No differences have so far emerged regarding haemorrhagic complications with any dose of streptokinase up to 10000 units h^{-1}. Lower doses of rtPA may be beneficial from this point of view[21].

The effectiveness of intra-arterial thrombolytic therapy in the management of the ischaemic limb is impressive. However, over half of the patients in this series were dealt with 'out of hours'. Close involvement between surgeons and radiologists is essential. The condition of the affected limb should be carefully monitored. Any deterioration, particularly resulting in neurological impairment, should be considered as an indication for alternative treatment.

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288–292

Randomized study on the effect of collagen impregnation of knitted Dacron® velour aortoiliac prostheses on blood loss during aortic reconstruction

Intraoperative blood loss is an important factor in reconstructive surgery for aortoiliac disease because it is clearly associated with an increase in the operative morbidity and mortality rates. To minimize intraoperative blood loss, a blood-tight vascular prosthesis has been developed by impregnating a knitted Dacron® prosthesis with bovine collagen. To study a potential reduction of intraoperative blood loss using these collagen-impregnated prostheses, we conducted a prospective randomized trial involving the collagen-impregnated prosthesis and its non-impregnated substrate, the Dacron knitted non-impregnated prosthesis. During a 2·5-year period, 123 consecutive patients (undergoing 81 procedures for aneurysmal disease and 43 procedures for occlusive disease) were admitted for elective aortic reconstructive surgery. Equal numbers of the two prostheses were randomly implanted. Various parameters were monitored: intraoperative blood loss before aortic cross-clamping (phase 1), during implantation of the prosthesis (phase 2) and after release of aorta cross-clamping (phase 3); the number of intraoperative and postoperative blood transfusions; and, finally, all preoperative and intraoperative factors that might contribute to intraoperative blood loss. A significant overall difference in intraoperative blood loss between the collagen-impregnated (2425 ml) and the non-impregnated (1907 ml) group was found (P=*0·003*). *However, this difference could not be attributed to collagen impregnation because no statistically significant difference in blood loss was found in the relevant period of operation (phase 3). Similar results were observed in patients operated on for both aneurysmal and occlusive disease (2600* versus *2195 ml and 2105* versus *1344 ml respectively).*

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Department of Surgery, University Hospital Leiden, The Netherlands
Correspondence to:
Dr J. H. Van Bockel, Department of Surgery, University Hospital, PO Box 9600, Leiden, The Netherlands

Many investigators have demonstrated that the incidence of postoperative morbidity and mortality after aortoiliac reconstruction is associated with a high amount of blood loss during surgery[1–6]. With low volumes of blood loss, the incidence of these complications is negligible. Blood loss should in any event be kept to a minimum because even the smallest amount of donor blood transfusion carries the risk of transmitting diseases such as hepatitis and acquired immune deficiency syndrome. The porosity of a vascular prosthesis at implantation is one of the factors influencing intraoperative blood loss. Blood may leak through the interstices of highly porous prostheses in spite of careful preclotting or in circumstances when preclotting cannot be performed adequately. Because of this some surgeons prefer a prosthesis with low porosity, e.g. woven Dacron® (E.I. du Pont de Nemours and Company, Wilmington, Delaware, USA), which obviates the need for preclotting and reduces interstitial bleeding. Others prefer the more porous knitted prostheses because of their better handling and healing characteristics[7,8]. To combine the superior healing characteristics of knitted Dacron prostheses with the benefits of a material that is impervious to blood, a knitted Dacron velour prosthesis impregnated with cross-linked bovine collagen has been developed. After implantation the collagen is absorbed and the knitted substrate with its advantageous healing characteristics remains[9,10].

This randomized study was conducted to evaluate whether collagen impregnation of Dacron prostheses reduces the amount of intraoperative blood loss during aortoiliac surgery.

Patients and methods

From September 1985 to March 1988, intraoperative blood loss was evaluated in 123 consecutive patients who underwent elective aortic reconstructive surgery. There were 112 men and 11 women of mean age 64 years (range 35–82 years). A total of 124 aortic reconstructions were evaluated: one patient was operated on twice.

The 124 reconstructions were performed using either a non-impregnated or a collagen-impregnated prosthesis. The non-impregnated prosthesis (the Microvel® Double Velour prosthesis (Meadox Medicals Incorporated, Oakland, New Jersey, USA)) was a knitted double velour Dacron prosthesis with a high water permeability of 1900 ml cm^{-2} min^{-1}. Prostheses with such a high porosity must be preclotted before implantation to prevent excessive blood loss[11]. This non-impregnated prosthesis has been used for many years and extensive experience has been obtained with it both at this and other institutions[12,13]. The collagen-impregnated prosthesis (the Microvel® Double Velour with Hemashield® prosthesis (Meadox Medicals Incorporated)) was similar to the non-impregnated prosthesis except that the knitted fabric had been impregnated with cross-linked bovine collagen to obtain zero porosity. Thus, preclotting of collagen-impregnated prostheses was not required. Collagen-sealed prostheses

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have been in development since the 1960s and have only recently become universally available[14].

Before operation, informed consent was obtained from each patient according to the procedure established by the Committee on Human Experimentation of the University Hospital of Leiden. Non-impregnated and collagen-impregnated prostheses were randomly assigned to the 124 cases by means of a table of random numbers generated by computer. The patients were stratified according to aneurysmal disease or occlusive disease, as it was anticipated that the type of the disease might influence the amount of blood loss. Due to this stratification, both impregnated and non-impregnated prostheses were evenly (and randomly) distributed within the two separate groups of diseases. This enabled a reliable study of the results in both the aneurysm group and the occlusive disease group Sixty-two reconstructions were performed using non-impregnated prostheses and 62 with collagen-impregnated prostheses. Eighty-one of the patients had aneurysmal disease and 43 had occlusive disease (*Table 1*)

Both the preoperative preparation of the patient and the operation itself were standardized to allow a reliable analysis of differences in blood loss between the two prostheses. Anticoagulant therapy (heparin followed by acenocoumarol) was used in all patients according to a standard protocol After release of the vascular clamps, the heparin effect was not reversed by protamine sulphate

The operation was performed via a midline laparotomy. Preclotting of the non-impregnated prostheses was performed by three consecutive soaks of the prostheses in 20 ml non-heparinized aortic blood (total 60 ml), stretching the prosthesis to ensure deposition of fibrin in the interstices Both the non-impregnated and the collagen-impregnated prostheses were implanted using monofilament sutures (Prolene®, Ethicon Ltd., Edinburgh, UK). A standardized procedure of flushing the prosthesis before removal of the vascular clamps was used.

To differentiate between prosthesis-related and non-prosthesis-related blood loss, blood loss was measured during three phases of the operation. Phase 1 was from the abdominal wall incision to cross-clamping of the aorta and included the exposure of the vessel segments for anastomoses and, when required, blood taken for preclotting of the non-impregnated prostheses. Phase 2 lasted from aortic cross-clamping until the clamp was released and included implantation of the prosthesis with one proximal and at least one distal anastomosis. Phase 3 comprised release of the aortic clamp until wound closure and included blood flow through the prosthesis Thus only during phase 3 could blood loss through the interstices of the prosthesis occur. Consequently, with the exception of blood taken for preclotting (phase 1), eventual differences in blood loss attributable to differences between the two prostheses should have become apparent in phase 3.

Throughout the study, blood loss and other characteristics of the operation were monitored and recorded by a trial co-ordinator after deliberation with, but independent of, the surgeon. During all three phases, blood loss was assessed from the weight of blood-soaked swabs and the volume of blood removed by suction Furthermore, the operative field was thoroughly cleared of blood before each new phase of the operation.

Other factors that might influence intraoperative blood loss were recorded (both preoperative and intraoperative). A history of previous aortoiliac operation was found in 19 cases (*Table 2*). The intraoperative events taken into consideration were bleeding related to the prosthesis itself (e g. through the interstices or at the suture line), bleeding from other origins (e.g. from lumbar arteries or other accidental surgical bleeding), simultaneous vascular procedures, occasional simultaneous non-vascular surgery (e g. cholecystectomy, sympathectomy, urethrolysis, nephrectomy, accidental splenectomy), type of prosthesis (tube, aortoiliac or aortofemoral), 'inlay' or end-to-end proximal anastomosis and, finally, experience of the surgeon. All but one of the preoperative and intraoperative factors were equally distributed between the groups of non-impregnated and collagen-impregnated prostheses (*Table 2*)

Table 1 *Relationship between type of disease and type of prosthesis used after stratification and randomization of 124 aortic reconstructions in 123 patients*

	No of prostheses		
Type of disease	Non-impregnated $(n=62)$	Collagen impregnated $(n=62)$	Total $(n=124)$
Aneurysmal disease	40	41	81
Occlusive disease	22	21	43

Table 2 *Distribution of preoperative and intraoperative factors potentially contributing to intraoperative blood loss in 124 aortic reconstructions*

	Type of prosthesis	
Factors	Non-impregnated	Collagen impregnated
Preoperative factors		
Revisional reconstruction	10	9
Prior abdominal operation	24	20
Intraoperative factors		
Prosthesis-related bleeding factors	4	4
Non-prosthesis-related bleeding factors*	17	7
Simultaneous vascular procedures	6	11
Simultaneous non-vascular procedures	12	7
Type of prosthesis		
Tube	16	11
Aortobi-iliac	27	32
Aortofemoral	19	19
Proximal anastomosis		
'Inlay'	24	24
End-to-end	38	38
Type of surgeon		
Vascular surgeon	44	45
General surgeon	7	9
Resident	11	8

* $P=0{\cdot}014$, all other differences between non-impregnated and collagen-impregnated prostheses are not statistically significant

Operative morbidity (e.g. myocardial infarction, multiorgan failure, adult respiratory distress syndrome, anaphylactic shock, infectious disease) and mortality were recorded. To determine the clinical implications of a reduction of intraoperative blood loss during the three phases, the amount of donor blood administered to the patient was measured. Finally, the number of units of blood transfused after operation was recorded.

Differences of means between groups were evaluated using the Mann–Whitney U test and one-way analysis of variance when appropriate Contingency tables were evaluated using the χ^2 and Fisher tests

The following financial data are worthy of note The trial co-ordinator was officially engaged by the University of Leiden Fifty per cent of the trial co-ordinator's salary was reimbursed by a grant from a sponsor and the other 50 per cent came from a grant from the Dutch Heart Foundation. All vascular prostheses were bought at commercial rates without any price reduction or gifts.

Results

The collagen-impregnated prosthesis was found to be blood-tight without preclotting. Clinically obvious leakage of blood through the interstices of the prosthesis after implantation was observed in only one collagen-impregnated prosthesis but in three non-impregnated prostheses, in spite of preclotting (*Table 2*). All bleeding was easily stopped by compression with swabs and, consequently, blood loss due to leakage through the prosthesis was limited Microscopic examination of a specimen of the collagen-impregnated prosthesis in question revealed no specific cause for leakage Graft thrombosis did not occur.

Overall, intraoperative blood loss was reduced in the collagen-impregnated group compared with the non-impregnated group. The mean intraoperative blood loss in the non-impregnated group was 2425 ml compared with 1907 ml in the collagen-impregnated group, a difference of 518 ml ($P=0{\cdot}003$) (*Figure 1*).

Analysis of intraoperative blood loss in the three phases of the operation revealed that the difference in overall blood loss could not be explained by collagen impregnation of the vascular

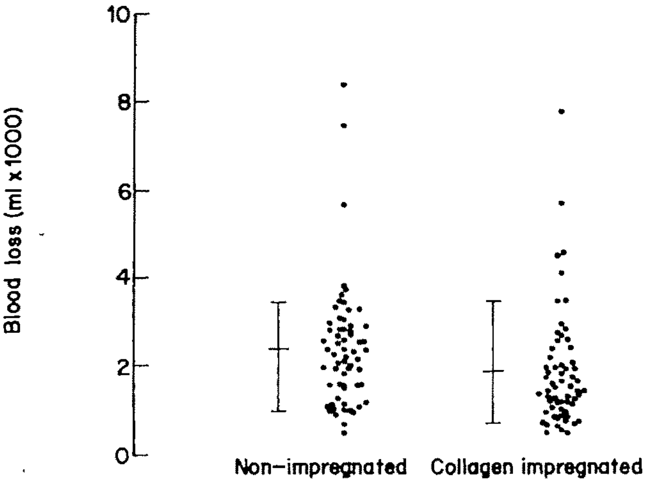

Figure 1 *Scattergram showing overall blood loss in procedures with non-impregnated prostheses* (n=*62*) *compared with blood loss in procedures with collagen-impregnated prostheses* (n=*62*). *Mean values are indicated together with tenth and 90th percentiles,* P=*0·003 non-impregnated* versus *collagen impregnated*

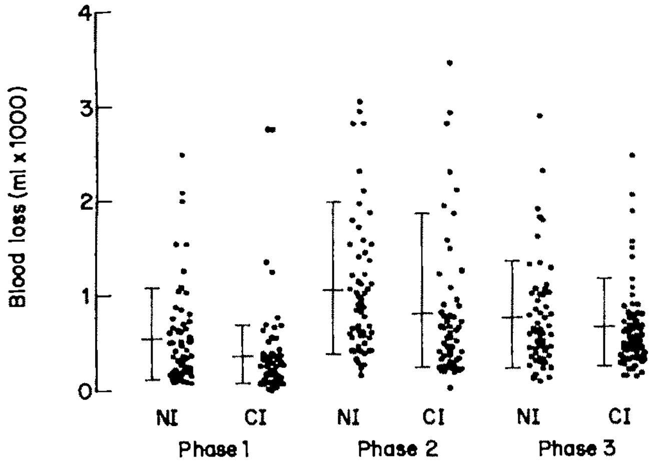

Figure 2 *Scattergram showing blood loss in 62 procedures with non-impregnated prostheses* (*NI*) *compared with blood loss in 62 procedures with collagen-impregnated prostheses* (*CI*) *during the three phases of the operation. Mean values are indicated together with tenth and 90th percentiles;* P=*0·001 phase 1 NI* versus *CI,* P=*0·004 phase 2 NI* versus *CI;* P=*0·39 phase 3 NI* versus *CI*

prosthesis. The difference in blood loss during phase three of the operation between the collagen-impregnated prosthesis and its non-impregnated substrate was not significant (*Figure 2*). Furthermore, the difference in blood loss in phase three (93 ml) was only a small part of the overall difference (518 ml). Finally, differences in intraoperative blood loss between both groups were observed not only in phase 3 but also in phases 1 and 2

In an attempt to analyse in more detail the differences in blood loss during phases 1 and 2, all cases in which significant blood loss due to non-prosthesis-related factors occurred (*Table 2*) were excluded. Thus, all potentially disturbing factors were excluded. For this analysis 55 collagen-impregnated and 45 non-impregnated cases were available. Once again, blood loss appeared to be reduced in the collagen-impregnated group: overall blood loss was 2124 ml in non-impregnated cases compared with 1848 ml in collagen-impregnated cases ($P<0·01$) (*Table 3*). However, once again, there were comparatively large differences in blood loss between the two groups in phases 1 and 2 which remain unclarified.

Comparing results in patients operated on for aneurysmal and occlusive disease, it was found that both overall blood loss and blood loss during the three phases showed similar results in aneurysmal (*Figures 3* and *4*) and occlusive disease (*Figures 5* and *6*). However, the overall difference in intraoperative blood loss between collagen-impregnated and non-impregnated groups in patients with aneurysmal disease was smaller ($P=0·07$).

As expected, this relatively modest reduction in blood loss (mean 518 ml) did not influence operative morbidity and

Table 3 *Intraoperative blood loss between procedures with non-impregnated and collagen-impregnated prostheses* (n=*100*), *24 procedures with non-prosthesis-related bleeding factors were excluded*

	Blood loss (ml)		
Phase of operation	Non-impregnated prosthesis ($n=45$)	Collagen-impregnated prosthesis ($n=55$)	*P*
Phase 1	497(407)	358(525)	0·001
Phase 2	917(500)	789(646)	0·02
Phase 3	710(362)	701(451)	0·60
Total	2124(872)	1848(1341)	0·01

Values are mean(s.d.)

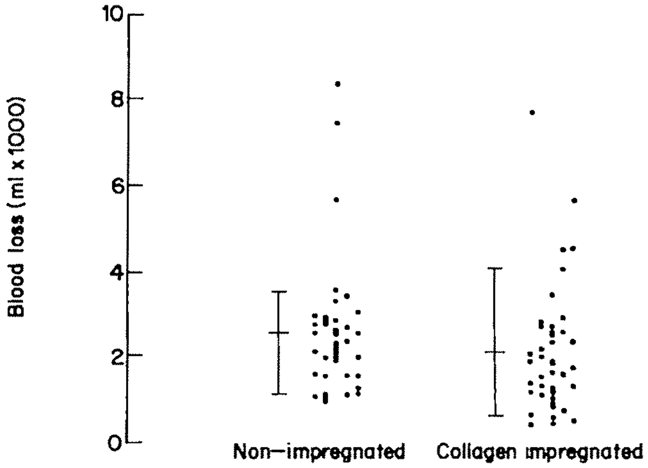

Figure 3 *Scattergram showing overall blood loss in procedures with non-impregnated prostheses* (n=*40*) *compared with blood loss in procedures with collagen-impregnated prostheses* (n=*41*) *for aneurysmal disease. Mean values are indicated together with tenth and 90th percentiles,* P=*0·07 non-impregnated* versus *collagen impregnated*

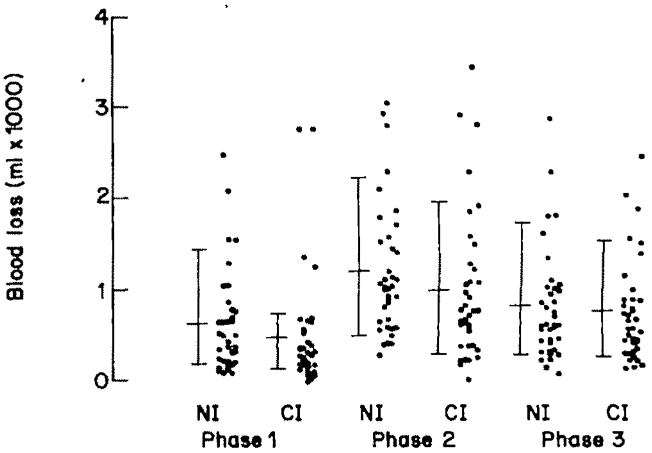

Figure 4 *Scattergram showing blood loss in 40 procedures with non-impregnated prostheses* (*NI*) *compared with blood loss in 41 procedures with collagen-impregnated prostheses* (*CI*) *during the three phases of operation for aneurysmal disease. Mean values are indicated together with tenth and 90th percentiles,* P=*0·02 phase 1 NI* versus *CI,* P=*0·05 phase 2 NI* versus *CI;* P=*0·7 phase 3 NI* versus *CI*

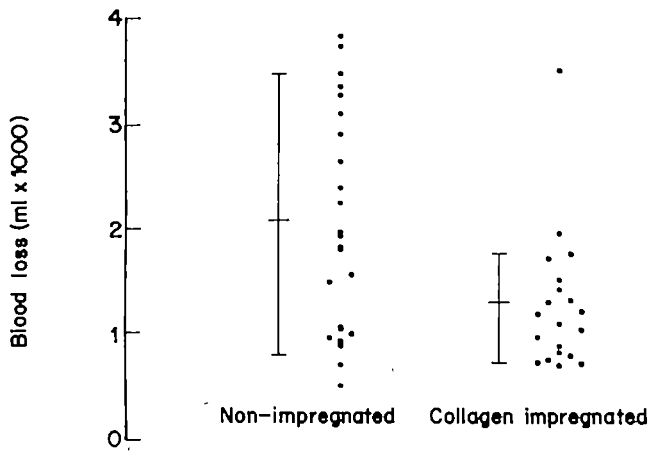

Figure 5 *Scattergram showing overall blood loss in procedures with non-impregnated prostheses* (n = *22*) *compared with blood loss in procedures with collagen-impregnated prostheses* (n = *21*) *for occlusive disease. Mean values are indicated together with tenth and 90th percentiles;* P = *0·02 non-impregnated* versus *collagen impregnated*

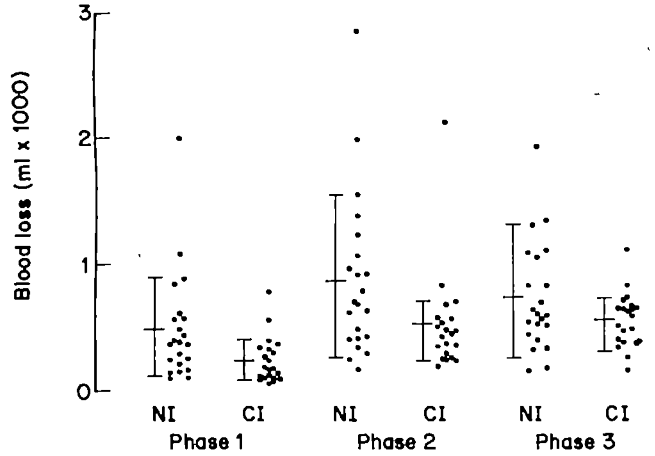

Figure 6 *Scattergram showing blood loss in 22 procedures with non-impregnated prostheses* (*NI*) *compared with blood loss in 21 procedures with collagen-impregnated prostheses* (*CI*) *during the three phases of operation for occlusive disease. Mean values are indicated together with tenth and 90th percentiles;* P = *0·01 phase 1 NI* versus *CI,* P = *0·03 phase 2 NI* versus *CI;* P = *0·3 phase 3 NI* versus *CI*

mortality rates. Six patients (5 per cent) died after operation, three in each group. Five patients had a myocardial infarction after operation, three in the non-impregnated and two in the collagen-impregnated group. No anaphylactic reactions or graft infections secondary to the prosthesis or donor blood transfusions were observed. As anticipated, the mortality rate was not related to the volume of blood loss; the average volume of blood loss in patients who died was not significantly different from that in patients who survived (2455 *versus* 2151 ml; $P > 0·3$).

The overall reduction in intraoperative blood loss was paralleled by a reduction in the number of donor blood transfusions (*Table 4*). During the operation, significantly less donor blood was given to patients receiving a collagen-impregnated prosthesis (*Table 5*), whereas during the post-operative period the volume of donor blood transfused was similar in both groups (*Table 4*).

Discussion

Only a limited number of studies on the effect of impregnation of prostheses on blood loss during aortic surgery have been performed. Most have evaluated the effect of collagen impregnation[13,15–17]. The authors reported that mean blood loss was reduced by 300–1165 ml. However, all but one of these studies were inconclusive for several reasons. First, the method of measuring the amount of blood was not described adequately. Second, the authors did not describe the preclotting technique employed. It is well known that preclotting makes a porous Dacron prosthesis impervious to blood[18]. Recently, Snooks *et al.*[11] demonstrated that a third soak in blood does not reduce the porosity any further. We have employed a three-stage technique which is therefore sufficient in this respect. Third, some investigators took into account only the number of donor blood transfusions, which is an inappropriate estimation of blood loss in a blood loss specific study[13,15]. Fourth, blood loss was never measured by an independent researcher such as a trial co-ordinator. In the present study, blood loss seems to be higher than in other studies[13,16,17,19]. There are several explanations for this. The blood loss measured by the co-ordinator was invariably higher than the amount estimated by the surgeon or anaesthetist, the method generally employed in other studies. A further explanation might be that our institution is a referral hospital. Therefore, a relatively high proportion of patients were admitted for revisional reconstructions, which are associated with more blood loss than primary reconstructions. Finally, almost all information on the effect of collagen impregnation of Dacron prostheses on blood loss has been obtained from retrospective studies[15,16]. In such studies other factors contributing to intraoperative blood loss may not be equally distributed between the groups, which confuses the interpretation of results. To our knowledge, only Harris[17] has conducted a prospective randomized study. They considered aortofemoral bypasses for occlusive disease exclusively and found no differences between the two prostheses, either in blood loss or in the number of units of transfused donor blood[17]. However, the results from that study should also be interpreted with caution, as there were more simultaneous procedures performed in the collagen-impregnated group and the number of patients included in the study was small.

Table 4 *Total number of units of donor blood transfused in patients with non-impregnated and collagen-impregnated prostheses*

	No. of units* of blood transfused		
Stage in transfusion	Non-impregnated prosthesis (*n* = 62)	Collagen-impregnated prosthesis (*n* = 62)	*P*
During operation	3·9(2·5)	2·8(2·8)	0·005
After operation	1·7(4·3)	1·9(4·1)	0·58
Total	5·6(5·5)	4·7(5·7)	0·07

Values are mean(s.d.); * mean volume per unit was 400 ml

Table 5 *Volume of donor blood transfused during aortic procedures with non-impregnated and with collagen-impregnated prostheses* (*all procedures included*)

	Volume of blood transfused (ml)		
Type of disease	Non-impregnated prosthesis (*n* = 62)	Collagen-impregnated prosthesis (*n* = 62)	*P*
Aneurysmal disease	1000(1040)	1300(1269)	0·11
Occlusive disease	1417(905)	824(758)	0·03
Total	1541(991)	1138(1135)	0·005

Values are mean(s.d.)

The present results seem to confirm the findings of other investigators with regard to reduction of intraoperative blood loss by collagen impregnation[15,16]. However, the analysis of blood loss in three phases enabled an assessment of the causal relationship between blood loss and porosity. To our surprise, we found a significant difference in intraoperative blood loss during phases 1 and 2 but not during phase 3 (the phase that was relevant to prosthesis-related blood loss). An explanation for this observation might have been that a potential difference in blood loss between the two groups in phase 3 may have been obscured by the higher volume of blood loss during phases 1 and 2. However, statistical analysis demonstrated that no correlation in volume of blood loss between phases 1 and 2, between phases 2 and 3, or between phases 1 and 3 occurred. Consequently, one must conclude that any reduction in blood loss found in patients with a collagen-impregnated prosthesis cannot be explained by collagen impregnation. It seems reasonable to expect that a significant difference in blood loss during phase 3 will be found when the number of patients in the study is increased. However, the authors feel that this additional effort is not justified because the small difference observed in phase 3 is not clinically relevant.

The overall difference in intraoperative blood loss between collagen-impregnated and non-impregnated groups in patients with aneurysmal disease was less ($P = 0{\cdot}07$) than in those with occlusive disease. That mean blood loss is considerably higher during aneurysm resection than during reconstruction for occlusive disease has been demonstrated by others[18] and can be explained by the occasional ample bleeding from lumbar arteries after opening the aneurysm.

The present study is the only evaluation so far of collagen impregnation on blood loss, in which blood loss could causally be related to the porosity of the prosthesis. However, in spite of the relatively large number of patients, it was not proven that collagen impregnation reduces blood loss. Furthermore, the conclusions of others that impregnation reduces operative blood loss should be interpreted with caution Finally, we conclude that collagen impregnation appears to be a safe and convenient innovation when a blood-tight prosthesis is preferred, for instance in heparinized patients and for ruptured aneurysm surgery

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Gastrointestinal complications in 4473 patients who underwent cardiopulmonary bypass surgery

S. P. J. Huddy,
W. P. Joyce and
J. R. Pepper

South West Thames Regional Cardiothoracic Unit, St. George's Hospital, London SW17 0RE, UK
Correspondence to:
Mr S. P. J. Huddy

Thirty-nine gastrointestinal complications occurred in 35 of 4473 patients (0·78 per cent) who underwent surgery involving cardiopulmonary bypass during an 8-year period. The mortality rate when one of these complications occurred was 22 (63 per cent) representing 11·5 per cent of the 191 deaths from all causes in the series. The relative risk of developing a gastrointestinal complication was 1:249 when the heart was not opened, 1:66 when it was and 1:5 after cardiac transplantation. Gastrointestinal bleeding (n = *20) was the most common complication of whom nine (45 per cent) died, followed by intestinal infarction* (n = *12) with eight (67 per cent) deaths and acute pancreatitis* (n = *6) all of whom died. There was one death after surgery for gastrointestinal bleeding* (n = *7). No patient survived bowel infarction without operation but resection was possible in five of the eight who underwent surgery, four of whom survived. The results demonstrate that surgical intervention is not associated with undue mortality but inappropriate conservative therapy is poorly tolerated in this high-risk group.*

It is well recognized that patients who undergo surgery involving the use of cardiopulmonary bypass occasionally develop abdominal complications and that the mortality is then high[1–7]. These patients present a difficult management problem. They often have multisystem disease and may be receiving multiple drug therapies (e.g. paralysing agents, inotropes, opiate analgesics or immunosuppressants) which make accurate assessment difficult They may be unable to describe symptoms or react to examination. The equipment associated with modern intensive care makes movement of the patient around the hospital for investigation or treatment difficult and hazardous. In addition there is a reluctance on the part of the managing physicians to consider invasive diagnostic techniques or operative intervention.

In an attempt to clarify the factors which predispose to these complications, and the optimum management of the patients, all patients who have undergone surgery involving the use of cardiopulmonary bypass in a single unit during an 8-year period have been reviewed retrospectively.

Patients and methods

All patients who underwent surgery involving bypass between November 1980 and August 1988 were included in the study During these years data concerning the pre-, intra- and postoperative status of these patients were collected on an extensive proforma. Included on this proforma was the presence or absence of an abdominal complication. The patients who developed a major abdominal complication were identified and more detailed information was collected from the hospital notes For comparison, data from the proforma were also analysed for all 4473 patients who underwent similar surgery during this time.

All gastrointestinal complications were included in the study. A gastrointestinal bleed was only included if there was an associated haemodynamic disturbance or a requirement for transfusion. Hyperamylasaemia alone was not an indication for inclusion. Acute pancreatitis was diagnosed if there were the clinical features of pancreatitis together with either hyperamylasaemia or histological proof

The data from the group of patients who developed gastrointestinal complications were compared with the group who did not using the Student's t test or the χ^2 test with Yates' correction where appropriate A P value of $<0{\cdot}05$ was taken to indicate statistical significance

Results

A total of 4473 patients underwent surgery involving cardiopulmonary bypass during the period studied. There were 39 abdominal complications which occurred in 35 patients (0·78 per cent). Twenty-two of the 35 patients who developed gastrointestinal complications died giving a mortality rate of 63 per cent compared with a mortality rate of 3·8 per cent for the 179 deaths among the patients who did not develop this complication ($P<0{\cdot}001$). These deaths accounted for 11·5 per cent of the deaths from all causes in the series

Preoperative, bypass and postoperative parameters for the patients who developed abdominal complications are listed in *Tables 1, 2* and *3* respectively, together with the same parameters for those who did not have complications. *Table 4* lists the type of cardiac operations performed and the abdominal complications encountered are detailed in *Table 5*

Gastrointestinal bleeding was the largest group occurring in 20 patients. The gastrointestinal bleeds occurred between 2 and 25 (median 10) days after the initial bypass procedure. The causes, management and outcome are listed in *Table 6*. In six patients a significant gastrointestinal bleed occurred but the site of bleeding was not investigated usually due to complex multisystem problems. One of these had a single major bleed and then made an otherwise uncomplicated recovery on H_2 antagonists. The other five all died. In two a clotting disorder was probably contributory, one had a brisk haematemesis and subsequently died with fresh bleeding from both ends of the gastrointestinal tract and two died of continuing haematemesis and melaena.

Thirteen patients were treated conservatively for a gastrointestinal bleed of whom eight (62 per cent) died. In six the source of the bleeding was not investigated and five (83 per cent) died. In seven the bleeding site was investigated and located, conservative treatment was continued and three (43 per cent) died. One (14 per cent) of the seven treated surgically died. The cause of death in eight patients treated conservatively was: massive haemorrhage in one, continued bleeding in three, multisystem failure secondary to hypotension consequent upon bleeding in one, arrhythmia in one, bowel ischaemia in one and multisystem failure without hypotension

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Table 1 *Preoperative variables of the 35 patients who developed gastrointestinal complications and 4438 who did not after surgery involving cardiopulmonary bypass*

	Patients with gastrointestinal complications ($n=35$)	Patients without gastrointestinal complications ($n=4438$)	*P*
Mean(s d.) age	63 7(15·4)	57·0(12·9)	n.s.
Male:female ratio	5·1	3:1	n.s.
Urgency			
Emergency	9 (26)	276 (6 2)	
Urgent	9 (26)	998 (22·5)	<0·001
Routine	17 (49)	3163 (71 3)	
Redo operation	7 (20)	197 (4·4)	<0 001
On inotropes	5 (14)	84 (1·9)	<0 001
Renal failure (urea >20 mmol/litre)	10 (29)	70 (1·8)	<0 001
Respiratory disease	2 (6)	60 (1·4)	n s.
Intra-aortic balloon pump	2 (6)	33 (0 7)	<0·02

n s., Not significant. Values in parentheses are percentages

Table 2 *Bypass details of the 35 patients who developed gastrointestinal complications and 4438 who did not after surgery involving cardiopulmonary bypass*

	Patients with gastrointestinal complications ($n=35$)	Patients without gastrointestinal complications ($n=4438$)	*P*
Bypass time (min)			
>120	6 (17)	359 (8·1)	
30–120	29 (83)	4001 (90·2)	n s
<30	0	78 (1 8)	
Core temperature on bypass (°C)			
≤20	4 (11)	223 (5·0)	
21–30	9 (26)	799 (18 0)	n s.
31–36	22 (63)	3383 (76·2)	
37	0	33 (1·0)	
Use of pulsatile flow	8 (23)	2352 (53·0)	<0·001

n.s , Not significant. Values in parentheses are percentages

Table 3 *Postoperative variables of the 35 patients who developed gastrointestinal complications compared with 4438 patients who did not after surgery involving cardiopulmonary bypass*

	Patients with gastrointestinal complications ($n=35$)	Patients without gastrointestinal complications ($n=4438$)	*P*
Required intra-aortic balloon pump	9 (26)	138 (3·1)	<0 001
Ventilated for more than 12 h	22 (63)	496 (11·2)	<0 001
Developed renal failure (urea >20 mmol/litre)	19 (54)	132 (3·0)	<0·001
Required inotrope support*	19 (54)	433 (9·8)	<0 001
Required reoperation for bleeding	9 (26)	164 (3 7)	<0 001

Values in parentheses are percentages; * excludes 'renal dose' (≤5 μg/kg/min) dopamine

in one case. The single death in the group treated surgically was due to subsequent bowel infarction detected at post-mortem examination. All the patients who underwent surgery had suffered at least a second bleed or had continued bleeding before the operation was performed.

Eight of the 12 (11 definite and one probable) patients with ischaemic bowel died (mortality rate of 67 per cent). There was often a considerable delay between the onset of symptoms and the diagnosis being made. We have estimated from the notes the time from the probable onset of symptoms until diagnosis. The onset ranged from 1–16 (median 4) days after bypass, and the delay until diagnosis was another 0–13 (median 2) days. The delay in diagnosis in the four patients who survived with ischaemic bowel was 0, 0, 1 and 1 day respectively.

Nine of the patients with ischaemic bowel presented with abdominal distension, pain and tenderness, two with gastrointestinal bleeding and one with a general deterioration associated with bloody diarrhoea. The presentation was often insidious over a few days. At operation some patients had extensive gangrene of the small and large bowel and occlusion of larger vessels. However others had a patchy ischaemia (with or without gangrene) with pulsation present in major vessels. In four patients no operation was performed and these all died. Eight underwent laparotomy and in five a resection was possible of whom four survived to discharge from hospital alive and well and on a normal diet. The three patients in whom resection was not attempted all died.

Table 4 *The types of cardiac operation performed and the relative risk of developing a gastrointestinal complication* (P<*0·001*)

	Patients with gastrointestinal complications ($n=35$)	Patients without gastrointestinal complications ($n=4438$)	
Heart not opened	13	3234	1.249
Heart opened	18	1184	1·66
Cardiac transplant	4	20	1·5

Table 5 *The gastrointestinal complications which occurred in 35 patients following cardiopulmonary bypass operations*

Complication	No of cases
Bleeding gastric or duodenal erosions	3
Bleeding gastric ulcer	3
Bleeding duodenal ulcer	6
Gastrointestinal bleed (site not investigated)	6
Perforated duodenal ulcer	1
Acute pancreatitis	6
Ischaemic bowel	12
Pseudomembranous colitis	2
Peritonitis (cause unknown – see text)	1

Table 6 *The diagnosis, treatment and outcome in 20 patients who developed a gastrointestinal bleed after cardiopulmonary bypass surgery*

Diagnosis	Treatment	Outcome
Gastric and/or duodenal erosion ($n=3$)	All treated conservatively	Two died
Gastric and/or duodenal ulceration ($n=9$)	Five underwent operation (four Polya gastrectomy, one vagotomy)	One died
	Four treated conservatively	One died
Ischaemic small or large bowel ($n=4$)	One small bowel resection One large bowel resection Two small bowel infarction	Alive Alive Diagnosed at post-mortem
Site of bleeding not investigated ($n=6$)	All treated conservatively	Five died

One patient had both a duodenal ulcer and small bowel ischaemia, and one both erosions and small bowel ischaemia

One further patient died 3 days after cardiopulmonary bypass. Her postoperative course was complicated by rhythm disturbances, hypotension and renal failure Insertion of a peritoneal dialysis catheter revealed foul purulent peritoneal fluid. The cause of this peritonitis was not determined.

There were six cases of acute pancreatitis diagnosed by our criteria. These presented beween 1 and 23 (median 4) days after bypass. All of these six patients died.

One patient developed a perforated duodenal ulcer 10 days after cardiopulmonary bypass which was treated surgically by simple oversewing, from which he made a rapid recovery on H_2 antagonists

Two patients developed a pseudomembranous colitis. Both of these also had another gastrointestinal complication, one a gastrointestinal bleed and the other a gastrointestinal bleed and ischaemic bowel. Neither was immunosuppressed and both patients died.

The immunosuppresion of the cardiac transplant patients was achieved with a combination of cyclosporin and azathioprine, supplemented with steroids or antilymphocyte globulin for episodes of rejection. Two of the four patients in this group died without further surgery, one of pancreatitis and one of extensive mesenteric infarction. The other two underwent laparotomy, one patient had a Polya gastrectomy for a bleeding duodenal ulcer and the other had two laparotomies for a caecal perforation secondary to mesenteric ischaemia. Both of these patients survived to discharge from hospital.

Discussion

Gastrointestinal complications are uncommon after cardiopulmonary bypass, arising in less than 2 per cent of patients[1–7]. However, the mortality is high and in our series the 22 patients who died having suffered an abdominal complication represent 11·5 per cent of the deaths from all causes amongst the series. The early detection of these complications allows logical and potentially effective therapy, but the diagnosis is often difficult. The symptoms and signs of abdominal disease may be masked by drugs or the cardiac pathology and the development of the acute abdomen in this situation is often insidious and is detected late.

There is often a reluctance to submit patients to major abdominal surgery in the period immediately after cardiac surgery. However our results demonstrate that surgical intervention *per se* is not associated with an excessive mortality. No patient died as a result of the laparotomy itself. On the contrary, effective and well-timed intervention may be life-saving in patients who are poorly able to compensate for the major haemodynamic disturbances of the untreated abdominal condition.

Abdominal complications were more frequent in those patients who were severely ill before cardiac surgery but still almost half occurred in elective cases.

The majority of the complications seen after cardiopulmonary bypass may have an ischaemic aetiology[8,9]. However, whilst low cardiac output, shock and ischaemia can be shown experimentally to be associated with gastrointestinal mucosal damage[10], the abdominal complications seen after cardiopulmonary bypass are less common in similarly sick cardiac patients who have not undergone cardiac surgery. Other factors specific to the operation, such as microemboli which are known to occur[11–14], must play a part.

Opening the heart during surgery increases the potential for emboli. De-airing of the heart is a difficult and imperfect procedure and solid debris may be left within the chambers from the intracardiac procedure or the suture lines which provide a surface for platelet aggregation. In this study there was a markedly increased risk of a gastrointestinal complication after operations in which the heart was opened. Cardiac transplant recipients, who have the highest incidence of abdominal complications, have the greatest embolic potential as both sides of the heart are widely opened and there are long atrial suture lines for platelet and thrombus adhesion.

As in other studies gastrointestinal bleeding is the commonest abdominal complication seen in our series[2,4,6,7]. It has not been the policy of our unit to give routine peptic ulcer prophylaxis, but rather to give H_2 antagonists to those patients who had a history of peptic ulcer disease or who remained on the intensive care unit after the first day. The small number (12) of gastroduodenal bleeds (plus six gastrointestinal bleeds of unknown aetiology) amongst 4473 patients would seem to justify this approach.

There was only one death amongst the seven patients who underwent surgery for a gastrointestinal bleed whilst three of the seven in whom the source of bleeding was known and were treated conservatively died. The mixed bag of patients in each group does not allow strict comparison between the groups, but the severity of concurrent disease in the two groups was broadly similar although the conservatively treated group were on average approximately 10 years older The surgically treated group had more severe bleeding as all had had at least one re-bleed before operation, whilst four of the conservatively treated group had a single bleed which responded to treatment. No patient in the surgically treated group died or suffered significant morbidity as a result of the operation itself These results support the view that surgical intervention when appropriate is not contraindicated in the post-cardiac surgery period but rather that inappropriate continued conservative treatment is dangerous. These patients are poorly able to compensate for a rapid blood loss We would recommend immediate diagnostic endoscopy to make a definitive diagnosis and an aggressive surgical policy for patients who have a second bleed and possibly also for those who are found to have stigmata of recent haemorrhage at endoscopy (visible vessel or adherent clot) who have a high risk of further haemorrhage. A number of endoscopic techniques are currently being assessed in the treatment of acute gastrointestinal bleeding. These include injection of adrenaline or sclerosant, laser coagulation or diathermy coagulation. These may prove to be of value in post-bypass patients. Further data are necessary to evaluate this approach but they should be used with care in these patients who are haemodynamically unstable and in whom a general anaesthetic may prove to be a lesser risk than continued bleeding.

It is likely that the cases of acute pancreatitis which we found represent a major underestimate of the disease as the diagnosis is often difficult to make after cardiac surgery[15–17]. Hyperamylasaemia is common after cardiac surgery[18] but we only made a diagnosis of acute pancreatitis when this was accompanied by the clinical syndrome or pathological evidence of the disease. The 100 per cent mortality rate in our patients is probably a reflection of the many less severe and undiagnosed cases which may have been masked by the general condition of the patient. In a *post mortem* series Feiner[13] found a 16 per cent incidence of histologically proven pancreatitis and Haas *et al.*[17] a 25 per cent incidence. In severely ill patients there may be few specific features other than a general deterioration. The diagnosis should be considered in patients with unexplained deterioration or abdominal signs and appropriate investigation undertaken. However the treatment of this disease remains largely supportive at present, and the outcome after cardiac surgery poor[15,17].

Bowel ischaemia is relatively common after cardiac surgery and is a diagnosis to consider in this group of patients. The presentation is usually insidious, developing over several days rather than the acute presentation more commonly seen in general surgical practice. The patients typically develop a painless distension. Pain, vomiting and a general deterioration only appear later when gangrene has begun The gradual onset reflects the likely aetiology of the ischaemia which in many cases is not due to occlusion of major vessels but to patchy small vessel occlusion or spasm[19,20]. In these patients the ischaemia is likely to be due to low flow during cardiopulmonary bypass and/or microemboli within the splanchnic vasculature. This results in poor gut function with distension and increased luminal pressure which, in turn, causes a further reduction in mucosal blood flow. When seen at operation the infarction within the gut is typically patchy and resection is often possible preserving adequate intestinal length. Operation should not be ruled out because of the general condition of the patient as there were no survivors after conservative treatment. In five of eight patients who underwent laparotomy, resection was possible and four survived until discharge on a normal oral diet.

The diagnosis of mesenteric ischaemia is always difficult. Two recent reviews have examined the subject in detail[19,20]. Significant leucocytosis, unexplained acidosis, an increased serum phosphate or gastrointestinal blood loss are suggestive but non-specific[20,21]. Ultrasound, computed tomography, isotope scanning, endoscopy and laparoscopy are unhelpful in most instances. Angiography is the investigation of choice when the diagnosis has been considered. This may be definitive in occlusive disease and less certain in non-occlusive disease although here there is the possibility of pharmacological treatment at angiography[19,20]. In many cases, however, laparotomy must be undertaken on clinical suspicion alone as concrete evidence may not be available until the situation has become irreversible.

The incidence of abdominal complications in cardiac transplantation presents a special problem and the high incidence (4/24) in this series mirrors the experience of others[22,23]. The safety of laparotomy in post-transplant patients has also been previously noted[22]. Conservative treatment in this group has the additional problem of immunosuppression which both hinders the response of the patient to the disease and also provides a problem for the physician maintaining optimum drug levels in the sick, unstable patient. It may be that all cardiac transplant patients should have peptic ulcer prophylaxis in view of their particularly high risk (1:5) of developing an abdominal complication.

Pulsatile flow has been associated with a reduction in mortality, perioperative infarction rate, requirement for inotrope support and requirement for intra-aortic balloon pump support[24]. Murray *et al.*[25] demonstrated that the amylase/creatinine clearance ratio, used as a measure of pancreatic damage, was abnormal in nine of ten patients who underwent surgery using continuous flow bypass but in only one of ten using pulsatile bypass, a highly significant difference. Approximately half of our patients received pulsatile flow cardiopulmonary bypass but three-quarters of the abdominal complications came from the continuous flow group. The reduction in the number of abdominal complications with pulsatile flow may be due to the maintenance of splanchnic capillary blood flow during the perioperative period.

Abdominal complications after cardiac surgery provide a challenge for the surgeon. They differ from those encountered in ordinary general surgical practice, but when treated energetically and with a willingness to intervene promptly when necessary a successful outcome is frequently achieved. The results of inappropriate conservative treatment of these conditions are poor. There must be a greater awareness of the likely abdominal problems by the cardiac surgeon allowing detection at an early stage when they are often potentially curable. These patients are then best treated jointly with a group of general surgeons who regularly see post-cardiac surgery patients and thus can gain experience of the special problems involved.

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Isotopic study of the effects of platelets on development of intimal thickening in autologous vein grafts in dogs

T. Yukizane, K. Okadome, H. Eguchi, Y. Muto and K. Sugimachi

Second Department of Surgery, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812, Japan

Correspondence to:
Dr K. Okadome

The effects of platelets on the development of intimal thickening of arterially transplanted autologous vein grafts was investigated using canine poor run-off models. A new apparatus consisting of a shielding lead block to measure in vivo *platelet adherence only on the intima of the vein graft was developed. In 23 dogs, ^{51}Cr-labelled platelets (20 μCi/kg) were injected and isotope emission over the grafts was counted. Platelet adherence was expressed as the thrombocyte accumulation index (TAI), i.e. the ratio of counts over the graft under an abnormal flow condition in the poor run-off model to those over the graft under normal flow conditions of the contralateral leg. The TAI of the total graft (TTAI) was significantly high immediately and on the first and third days after implantation. The TAIs of the proximal (PTAI) and distal (DTAI) portions of the vein graft were also high at these same times. At 7, 10, 14 and 21 days, the TAI was almost equal to 1·0, a time at which endothelial regeneration was complete as confirmed by scanning electron microscopy. Thus, the prominent intimal thickening of arterially transplanted autologous vein grafts in dogs, induced under an abnormal flow condition, correlates well with the enhanced platelet adherence on the intima of the vein grafts in an early period after implantation.*

A major cause of late occlusion of autologous vein graft in reconstructive surgery for peripheral arterial disease is intimal thickening or hyperplasia of the graft[1–3]. Platelet-derived growth factor[4,5] is a cause of the fibrocellular hypertrophic lesion in an initial pathological change of arteriosclerosis, an event similar to the intimal thickening seen in autologous vein grafts.

We have reported that, in peripheral arterial reconstruction of the lower extremities, an electromagnetically determined flow waveform pattern correlated well with the outcome of the reconstructed artery[6]. In cases of a poor run-off and the type II flow waveform pattern late occlusions were frequent. The intima of the autologous vein graft was composed of fibromuscular hyperplasia consisting mainly of smooth muscle cells[7]. Morinaga *et al.* found that, under an abnormal condition of blood flow, intimal thickening was distinct within 1 month of grafting[8]. Endothelial disruption and successive interactions between platelets and the vascular wall are major events linked to intimal thickening of the graft.

We developed an *in vivo* method to measure platelet dynamics. A shielding lead block was devised to cut off radioactivity from the platelets in the tissue around the graft. The dynamic behaviour of platelets after placement of the autologous vein graft was observed. The correlation between intimal thickening and platelets in the development of intimal thickening, under conditions of an abnormal flow after grafting, was examined.

Materials and methods

Experimental model (Figure 1)

Forty-five mongrel dogs (10–15 kg) were anaesthetized with pentobarbital sodium (30 mg/kg) given intravenously. According to the method of Morinaga *et al.*[8], we first made a 7 cm incision on the medial aspect of the right thigh and ligated all branches in the popliteal area, except for the first branch of the distal caudal femoral artery, thus obtaining a model of poor distal run-off. Two weeks after the first operation, and at a time when collateral vessels were fully developed, we made a skin incision in the right thigh proximal to the previous incision and the femoral artery and vein were exposed. The femoral artery, 3 cm in length, was resected and replaced with a reversed femoral vein graft, 4 cm in length, in an end-to-end fashion with 7-0 polypropylene monofilament sutures. In the normal blood flow group, the autologous vein graft was implanted into the contralateral femoral artery under conditions of normal blood flow.

Haemodynamic measurement

After restoration of the blood flow through the autologous vein graft, the flow probe was applied on the midportion of the graft and the mean flow rate and flow waveform were measured using an electromagnetic flowmeter (Nihon Koden, MF-27, Tokyo, Japan). The data were simultaneously input into the waveform analyser, and variation of wall shear stress in a cardiac cycle (τ-variation) could be observed.

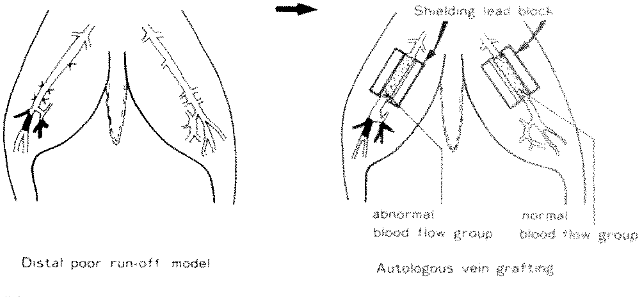

Figure 1 *Experimental set-up.* **a** *Distal poor run-off model;* **b** *autologous vein grafting*

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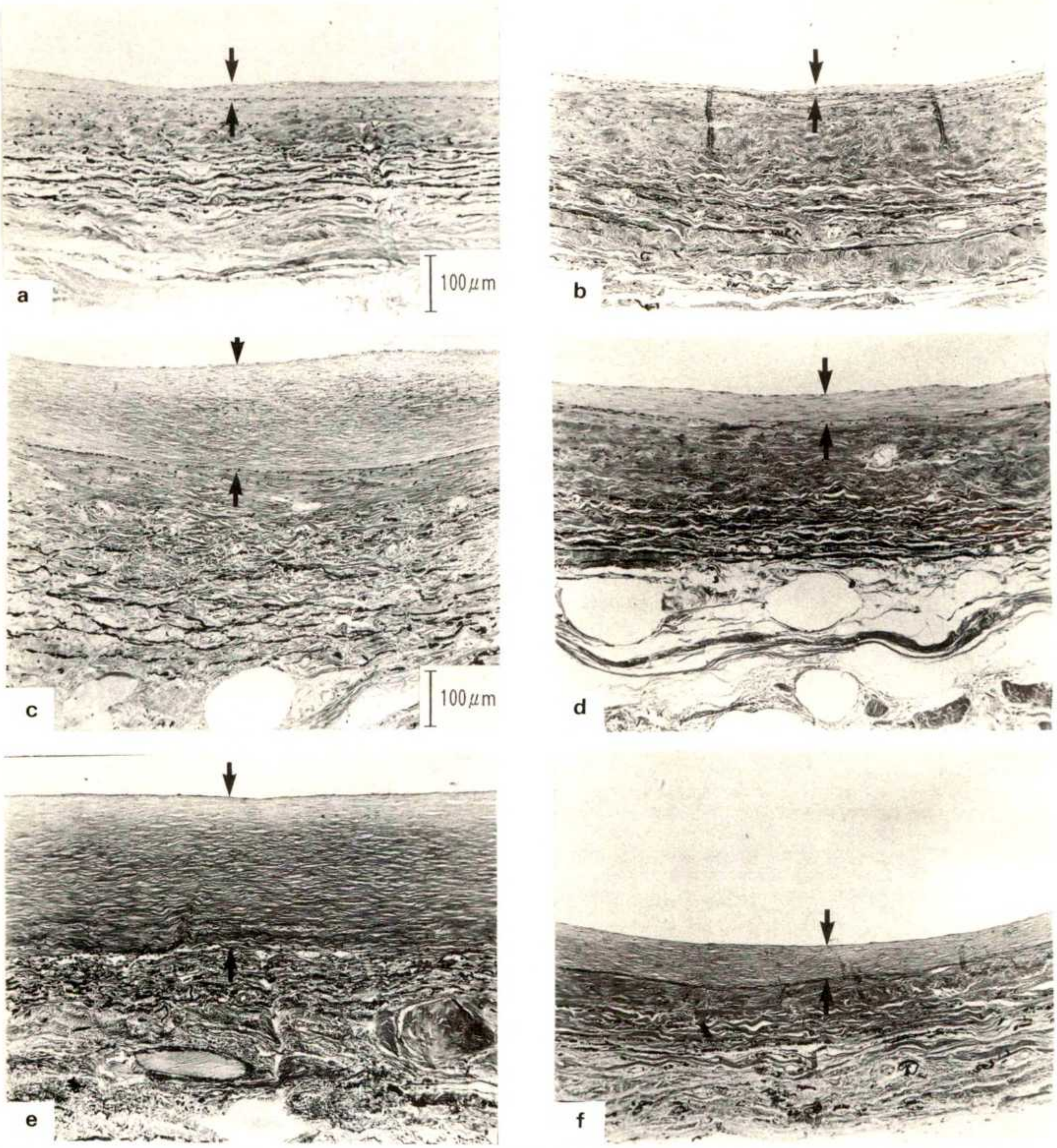

Figure 2 *Microscopic features of autologous vein graft at 7, 14 and 21 days after grafting:* **a, c, e** *under abnormal flow;* **b, d, f** *under normal flow;* **a, b** *day 7;* **c, d,** *day 14;* **e, f** *day 21. Intima is the area between the arrows (elastica van Gieson's stain, magnification × 100)*

Platelet isolation and labelling

According to procedures reported by the International Committee for Standardization in Hematology[9], platelet-rich plasma was obtained and labelled with $Na^{51}CrO_4$.

Protocol of measurements

The sample solution was added to 10 ml platelet-poor plasma and infused intravenously into the dogs 15 min before restoration of blood flow after grafting ($n = 5$) and on the first day ($n = 3$), the third day ($n = 3$), the seventh day ($n = 3$), the tenth day ($n = 3$), the 14th day ($n = 3$) and the 21st day ($n = 3$) after grafting, respectively. After grafting in each dog, ^{51}Cr-labelled autologous platelets were infused, and the grafts in the abnormal and normal blood flow groups of experimental dogs were scanned at regular intervals: 1 h, 3 h, 6 h, 12 h, 1 day, 3 days, 7 days, 10 days and 14 days after injection of the ^{51}Cr-labelled platelets.

In vivo *measurements*

To avoid radioactivity around the autologous vein graft, a shielding lead block was developed (*Figure 1*). This block was attached to the autologous vein graft and was 5·5 cm long and 4·5 cm wide. There was a groove with a width of 1·0 cm in the centre of the block, in which an autologous vein graft could be set. The graft was put on the shielding lead block and the block was fixed to the adjacent tissue by silk sutures. For *in vivo* measurements, we used a single counter/ratemeter, with a 5 × 5 cm thallium-activated sodium iodide crystal (M&S 310, J. and P. Engineering, Crawley, UK)[10]. The measuring apparatus crystal was

Table 1 *Data on haemodynamics*

	Flow rate (ml/min)	τ-variation (dyne/cm^2)
Abnormal flow ($n=53$)	15·5(10·4)*	68·9(35·9)†
Normal flow ($n=53$)	42·1(9·04)	198·5(107·4)

Values are mean(s.d.); * $P<0·05$; † $P<0·01$

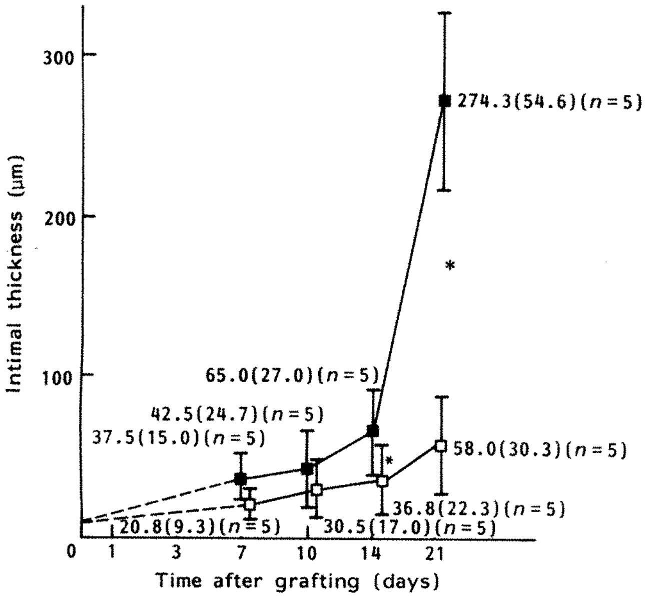

Figure 3 *Progression of intimal thickening;* ■, *abnormal flow condition;* □, *normal flow conditions;* * $P<0·05$

set at 2 x 2 cm, and the crystal was covered with a lead collimeter. The portion of the autologous vein graft which was between 0·5 cm proximal and 1·5 cm distal from the proximal anastomotic site was designated as the proximal site, and the distal portion from 1·5 cm proximal to 0·5 cm distal from the distal anastomotic site was designated as the distal site. Measurements were carried out on these two portions. To examine the reliability of use of the shielding lead block for *in vivo* measurements, a preliminary test was performed in two groups of three dogs each, with or without the shielding lead block, respectively. The measured counts were expressed as thrombocyte accumulation index (TAI) according to the following equation;

$$\mathrm{TAI} = \frac{\text{Measured counts of graft under abnormal blood flow condition}}{\text{Measured counts of graft under normal blood flow condition}}$$

Counts of the proximal and distal sites were expressed as proximal and distal TAI (PTAI and DTAI) respectively. Whole graft counts were expressed as total TAI (TTAI).

Morphological study

The autologous vein grafts in 15 mongrel dogs were resected on the seventh day ($n=5$), the 14th day ($n=5$) and the 21st day ($n=5$) after grafting. The specimens were fixed with 10 per cent buffered formalin solution and processed for light microscopy. Intimal thickening was measured by an ocular cytometer placed on the ocular lens of a light microscope at a final magnification of 100 and measured at six arbitrary points with a micrometer. Statistical comparison of the intimal thickening between abnormal and normal blood flow groups was made using Student's *t* test.

A scanning electron microscope study was made of the intima on the first day ($n=2$), the third day ($n=2$), the seventh day ($n=2$), the 14th day ($n=2$) and the 21st day ($n=2$) after grafting. The dogs were anaesthetized and a cannula was placed in the proximal site of femoral artery. A mixture of 1 per cent paraformaldehyde and 1·25 per cent glutaraldehyde in 0·1 mol/l cacodylate buffer pH 7·4 (Karnovisky's fixative, diluted 1:3)[11] was perfused through this cannula for 15 min at room temperature. Proximal anastomotic, distal anastomotic and midportions of grafts were removed intact and fixed overnight in 1:1 diluted Karnovisky's fixative. After washing in 0·1 mol/l cacodylate buffer, these segments were processed for scanning electron microscopy.

Results

Haemodynamic data (Table 1)

Flow rate and τ-variation in the abnormal blood flow group were significantly lower than in the normal blood flow group.

Progression of intimal thickening

The intimal thickness of the autologous vein graft on the seventh, 14th and 21st days after grafting is shown in *Figure 2*. Progression of intimal thickening was marked under conditions of abnormal flow compared with findings under normal flow conditions, with a statistical significance at the 14th ($P<0·05$) and 21st ($P<0·05$) days after implantation (*Figure 3*).

Platelet adherence in preliminary tests

The TTAI value, with and without use of the shielding lead block, is shown in *Figure 4*. The value without the block showed a prominent fluctuation during the entire observation period and was not reliable.

Platelet adherence to the autologous vein graft

From the data obtained using each dog, TTAI was calculated and the values are shown in *Figure 5*. TTAI showed significantly

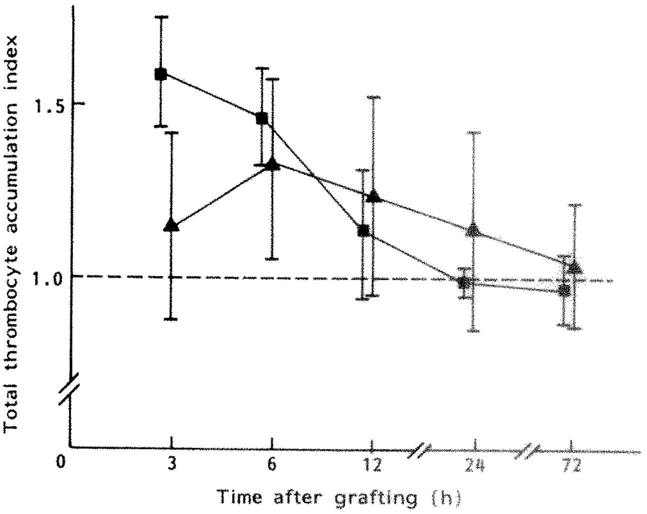

Figure 4 *Measurement of total thrombocyte accumulation index, with* (■) *or without* (▲) *the shielding lead block, at the preliminary test*

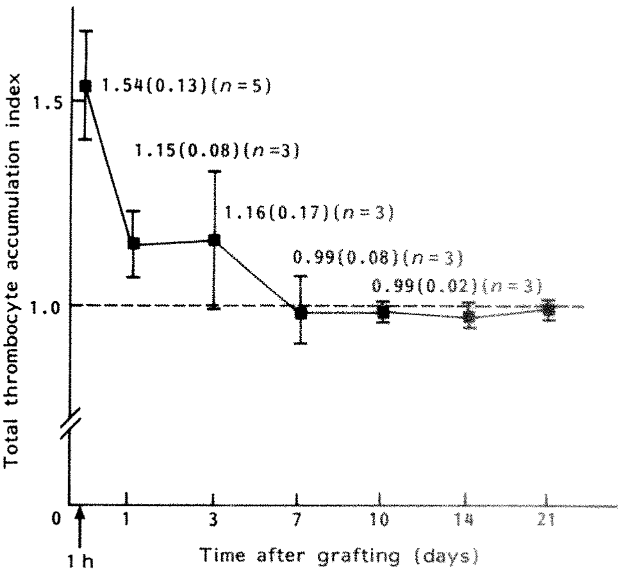

Figure 5 *Measurement of total thrombocyte accumulation index after implantation of autologous vein grafts*

Table 2 *PTAI and DTAI values*

	1 h after implantation ($n=5$)	Day 1 ($n=3$)	Day 3 ($n=3$)	Day 7 ($n=3$)	Day 10 ($n=3$)	Day 14 ($n=3$)	Day 21 ($n=3$)
PTAI	1·54(0·15)	1·16(0·07)	1·18(0·18)	0·97(0·12)	0·99(0·02)	0·97(0·04)	1·01(0·02)
DTAI	1·51(0·16)	1·11(0·04)	1·23(0·22)	0·99(0·06)	0·99(0·02)	0·99(0·02)	0·98(0·04)

Values in parentheses are s.d.; PTAI, proximal thrombocyte accumulation index; DTAI; distal thrombocyte accumulation index

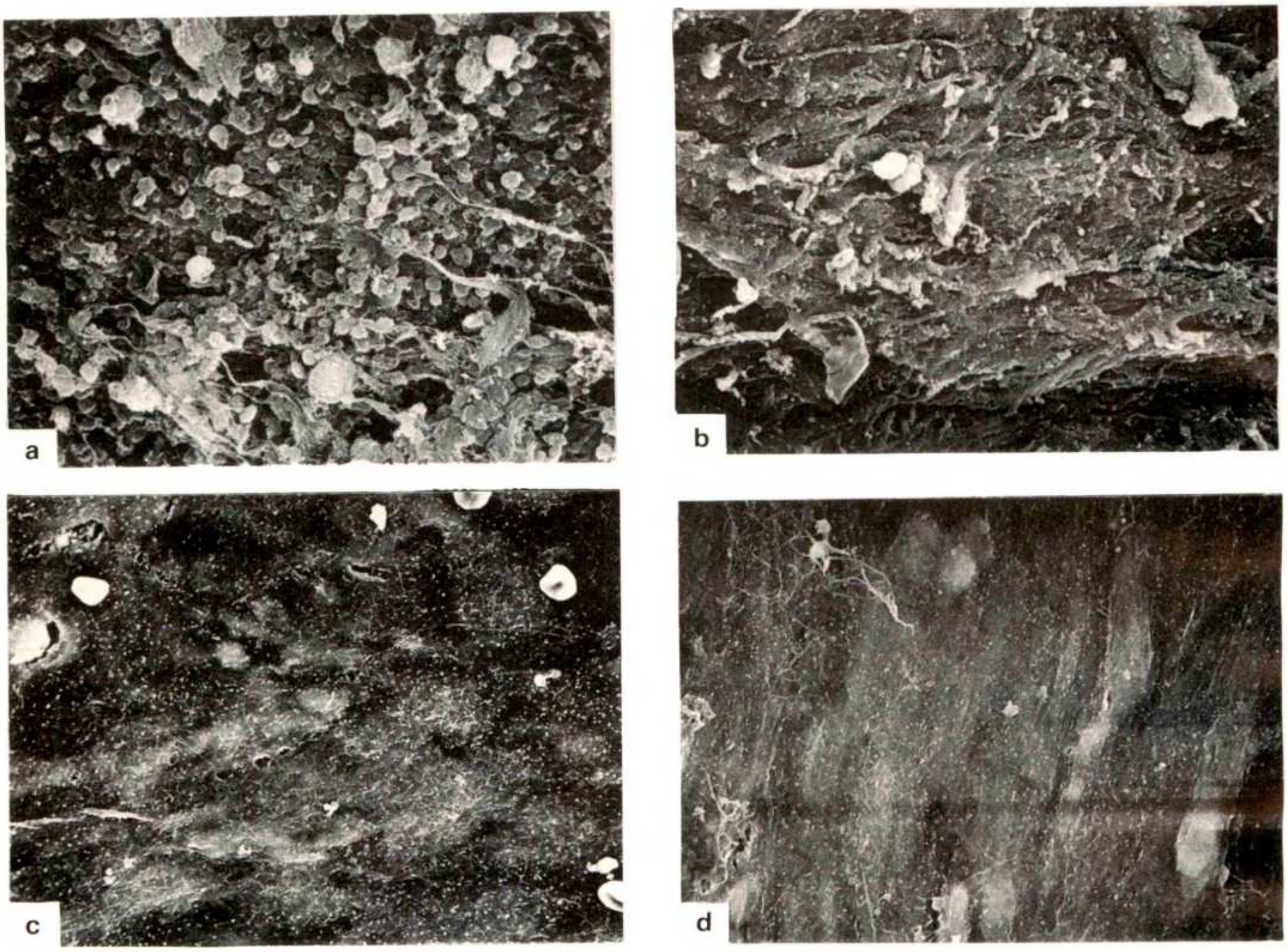

Figure 6 *Scanning electron microscopic features of autologous vein grafts;* **a, c** *abnormal flow group;* **b, d** *normal flow group;* **a, b** *day 1;* **c, d** *day 7 (magnification × 1500)*

higher mean(s.d.) values over 1·0 with 1·54(0·13) immediately after grafting, 1·15(0·08) at the first day and 1·16(0·17) at the third day. The adherence of platelets on the intima of the autologous vein graft in the abnormal blood flow group was higher than in the normal blood flow group within 3 days of the implantation. On the seventh day, TTAI showed a value of about 1·0. Thus, no statistically significant difference was noted between the abnormal and normal blood flow groups on the seventh day. Both PTAI and DTAI values were also high up to the third day, and on the seventh day reached almost 1·0 (*Table 2*).

Scanning electron microscopy findings

Observation of the internal surface of the autologous vein graft on the first day after grafting in both the normal and abnormal blood flow groups showed endothelial disruption and adherence of platelets and red blood cells on the subendothelial tissue (*Figure 6*). In the abnormal blood flow group, the adherence of platelets and red blood cells was more extensive than that seen in the normal blood flow group. On the seventh day after grafting, in both groups, regeneration and reconstruction of endothelial cells were apparent. However, the gaps between the endothelial cells were large and regeneration of the endothelial cells was incomplete. Platelet adherence was rare (*Figure 6*). At the 14th and 21st days after grafting, in both groups, endothelial cells were completely regenerated and covered the internal surface of the autologous vein graft. There was no adherence of platelets (*Figure 7*).

Discussion

For isotopic experiments on the dynamic behaviour of platelets, a scanning γ-camera or *in vitro* measurement of the extirpated samples can be used. Goldman *et al.* studied the correlation between labelled platelets and synthetic graft using the thrombogenicity index[12,13]. However, their *in vivo* measure-

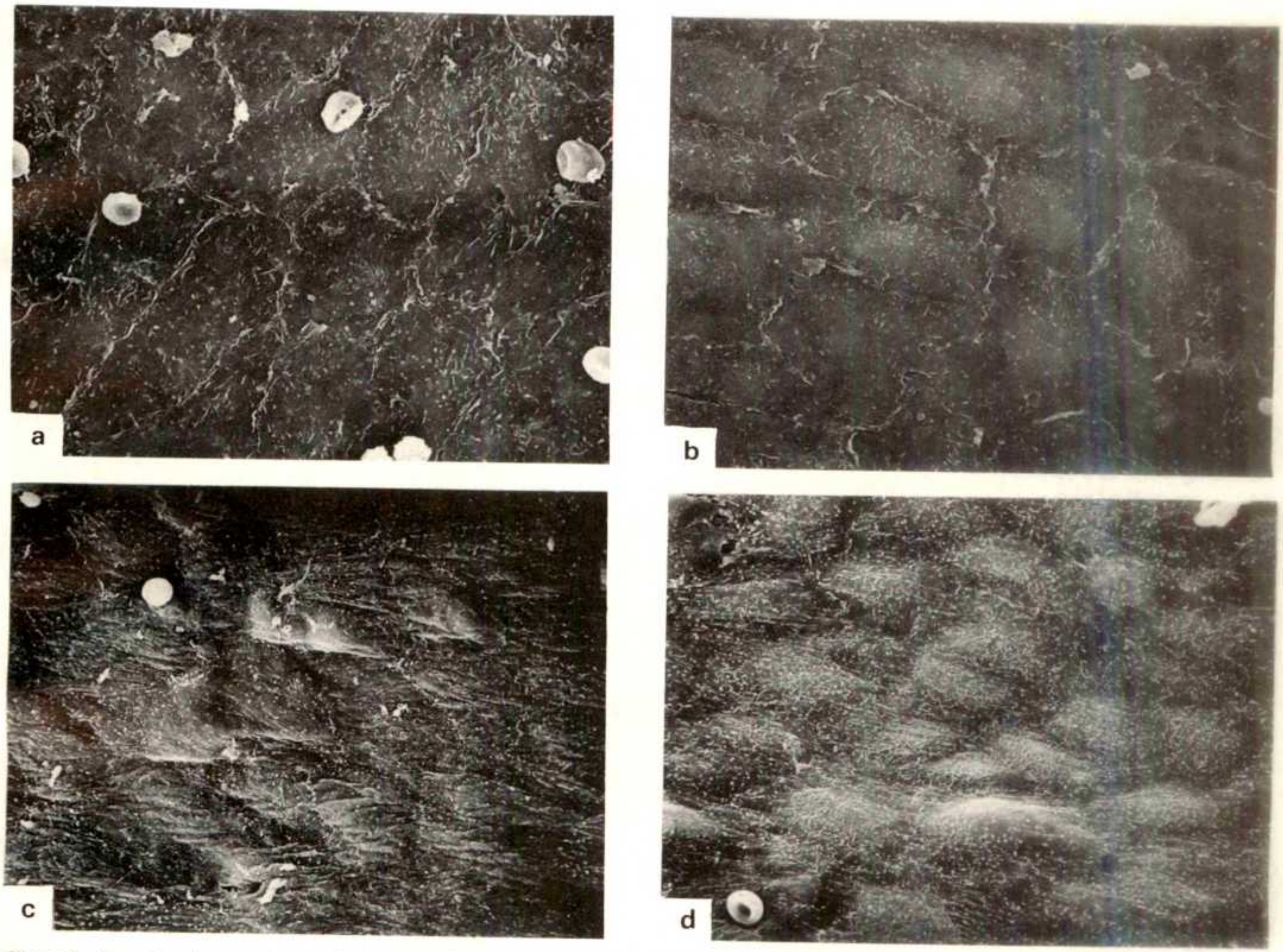

Figure 7 *Scanning electron microscopic features of autologous vein grafts;* **a, c** *abnormal flow group;* **b, d** *normal flow group;* **a, b** *day 14;* **c, d** *day 21 (magnification × 1500)*

ments included radioactivity of the labelled platelets in the tissue around the measured synthetic graft. The *in vivo* method used in the present study has the advantage that the level of radioactivity in the surrounding tissue can be attenuated to about one-fiftieth by using a shielding lead block, so improving the reliability of radioactivity measurement in the autologous vein graft and allowing a more precise assessment of the dynamic behaviour of platelets in the intima of the implanted autologous vein graft.

In peripheral arterial reconstructions, late occlusion of the autologous vein graft continues to perplex the surgeon[1,2,14]. Intimal thickening of the vein graft seems to be the main cause[15,16]. In previous studies, we found that reconstructed arteries with a haemodynamically abnormal flow waveform pattern were prone to late failure. Examination of the pathology of the grafts with an abnormal flow waveform in the follow-up period revealed that the intima of the autologous vein graft was thickened with fibrocellular proliferation, mainly composed of proliferation of smooth muscle cells with a rich intercellular fibrous matrix[7]. Morinaga *et al.* found that intimal thickening of the autologous vein graft could be rapidly induced within 1 month of implantation, but only when the blood flow conditions were abnormal[8].

Data on the relationship between intimal thickening of the autologous vein grafts under abnormal conditions of blood flow and platelet dynamics are scanty in the literature. Gershlick *et al.* found that the hyperaggregative state of platelets near the implanted autologous vein grafts in rabbits in the early months after operation seemed to be related to processes of intimal hyperplasia of the grafts[17]. Fuster *et al.* reported on the efficacy of antiplatelet drugs in reducing thickening of the intima of the aortocoronary arterial bypass graft in dogs, using the ^{111}In-labelled platelets counting method[18]. However, these investigations were performed under conditions of normal flow. We obtained evidence that the platelet adherence and the progression of intimal thickening were more prominent under conditions of abnormal flow.

In 1974, Ross *et al.* reported evidence for a platelet-derived growth factor[4], and in 1986 Ross noted the relationship between the mechanisms of generation of intimal thickening in arteriosclerosis and the role of platelets[19]. The effects of antiplatelet therapy on the results of aortocoronary bypass have also been reported[20,21]. Fuster and Chesebro described the relationship between improved results of autologous vein graft in an aortocoronary bypass and antiplatelet therapy, and the close correlation between intimal thickening and the platelet[22].

Also in the present study the intimal thickening was continuous after the 14th day of grafting, although the adherence of platelets was rare, even on the seventh day after grafting and at the time when endothelial cells were repaired or regenerated. Thus platelets seem to play an important role in the development of intimal thickening at an early stage and before regenerative repair.

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For debate

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Towards an appropriate training for vascular surgeons

S. J. Cawthorn and
A. E. B. Giddings

Royal Surrey County Hospital,
Egerton Road, Park Barn,
Guildford, Surrey GU2 5XX, UK
Correspondence to:
Mr A. E. B. Giddings

The increasing demand for fully trained vascular surgeons in the UK has highlighted the need for urgent review of that training. Such a review must examine the number of trainees required and the number and role of teaching centres. Vascular surgical training should only take place where an integrated approach, including experience in interventional radiology and intensive care, is available. The relationship of vascular to general surgery must now be defined with training needs in mind if we are to provide an appropriate service within the next decade.

A review of vascular surgical training in the UK is urgently required for two reasons: first, the current shortage of trained senior registrars to fill the consultant posts now being advertised, and second, the uneven availability of new techniques for the treatment of peripheral vascular disease. Proposals to formalize the experience of senior registrars in specialist vascular units have recently been set out for discussion by the Vascular Surgical Society of Great Britain and Ireland. This is an important move towards the definition of standards for accreditation in vascular surgery but it is only a beginning. No attempt has yet been made to define the number of trainees required, the skills which should be taught and where that teaching should take place.

The need for vascular surgeons to manage all patients with peripheral vascular disease, whether elective or emergency, has recently been highlighted[1]. This desirable change appears an impossible goal at present because there are so few trained vascular surgeons. The number required to provide an adequate service is a matter for some speculation, depending as it does on the relationship of vascular surgery to general surgery. However, as the specialty evolves in its own right, it is likely that we shall need at least as many vascular surgeons as urologists (perhaps two for every 250 000 patients), and a minimum of two for any hospital providing a vascular surgical service. One possible solution to this problem would be the centralization of all vascular services into specialist centres, not necessarily undergraduate teaching hospitals. Enthusiasts for this solution may claim that this could reduce both mortality and amputation rates in acute ischaemia[2]. However, the number of patients and the uneven distribution of such centres means that such an arrangement is impractical at present and it must be remembered that in an emergency, for example ruptured aneurysm, it is the availability of specialist consultant experience that is critical, not the location. Indeed, the report of a Confidential Enquiry into Perioperative Deaths demonstrated that the results of emergency aneurysm surgery were better in district general hospitals, where the surgeon was generally a consultant, than in teaching hospitals[3].

How has this situation arisen and what should be done? The present shortfall of trained vascular surgeons is the result of recent, but unplanned, consultant expansion in this specialty. If this expansion is to continue as it should, there must be a balancing increase in the number of registrars and senior registrars considerably above the number identified by the Joint Planning and Advisory Committee (JPAC), which has aimed only to balance training posts with vacancies due to retirement and death and to provide for very modest expansion. The JPAC numbers should be reviewed now, to take into account the diverging interests of general and vascular surgery in the next decade. This is not to imply that vascular surgery should be divorced from general surgery, but that a general surgeon with a special interest in vascular surgery requires a different training programme from that of a general surgeon with a special interest in, for example, gastroenterology.

Equally important is a review of the content of vascular training. Standard embolectomy, aortofemoral and femoropopliteal bypass is no longer an adequate repertoire for the vascular surgeon. The improved results of careful distal bypass[4], endoscopic sympathectomy[5] and thrombolysis[6] are examples of the benefits of greater specialization and an improving technology. These evolving techniques, which are sporadically available in district general hospitals and teaching hospitals alike, demand a new approach to training. The needs of the vascular surgeon can no longer be met by surgical training alone and, to keep pace with our advancing opportunities, experience within a multidisciplinary vascular team in a properly equipped unit is essential. The consultant vascular surgeon must understand the role and limitations of interventional radiology and the proper management of patients in the intensive care unit. Such experience is needed in vascular surgical training more than experience in, for example, urology or orthopaedics. The disciplines of intensive care, radiology and the vascular laboratory are as essential to the trainee as the teaching of a proficient surgical technique and the careful audit of results. How else, for example, will the value, indications and timing of thrombolysis be understood, and how else can the potential of both surgeon and radiologist be realized[7]? Improved results from intervention such as thrombolysis will be achieved only by team work in experienced units and it is an indication of the size of the problem that, despite its unique benefits, this technique is at present regularly practised in less than six centres throughout the UK[8]. Already, the committee of the Joint Council of the Society for Vascular Surgery and the International Society for Cardiovascular Surgery has included in its definition of vascular surgery several interventional radiological techniques, such as balloon and laser angioplasty[9]. These are also included in guidelines for awarding hospital privileges in vascular surgery in the USA. It must also be included in our training within the vascular unit. Both our limited resources and the need for the more appropriate training outlined above will demand the reorganization of vascular surgical services into three tiers based on the level of specialist surgical skill available. All district hospitals will require the support of a general surgeon who can identify the correct diagnosis and refer if appropriate. The middle tier should be a designated vascular unit with at least two surgeons who have a special interest in vascular surgery and can undertake a full elective and emergency workload. There will, however, be some patients whom they would prefer to be treated in a regional centre, particularly those with less common and more

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hazardous conditions, such as cerebrovascular disease or thoracoabdominal aneurysm. Referral of these less common but complex problems is important to concentrate experience and to improve results. In tertiary referral such as this, the provision of a high quality service is fundamental to the satisfactory training of senior registrars who will later become general surgeons with a special interest in vascular surgery in a district general hospital.

As with trauma, efficient management of emergencies demands specialization within a multidisciplinary team. Despite the recognition by the Royal College of Surgeons of England of deficiencies in trauma care at present, there are as yet no defined roles for the vascular surgeon in that team and guidelines for accreditation in vascular surgery have yet to be decided. The Vascular Surgical Society of Great Britain and Ireland has initiated an important review of vascular training. This should now be extended to examine both the number of trainees and their rotation through units which can provide them with an efficient and appropriate training. This is an urgent task if each district is to provide an adequate vascular service within the next decade.

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READERSHIP SURVEY

In April 1990 a questionnaire was inserted into all 2100 copies of *The British Journal of Surgery* destined for readers in Great Britain and Ireland; by August a response rate of 45 per cent had been achieved. Half the replies came from consultants, 14 per cent from senior registrars, 21 per cent from registrars and 8 per cent from senior house officers. Half of the respondents gave their main area of interest as gastroenterology, 36 per cent as general surgery, 22 per cent as vascular surgery, and 15 per cent as oncology. No other area of interest was mentioned by more than 6 per cent.

Overall, it was felt that specialty interests were well covered by the *Journal*, particularly so by gastroenterologists and generalists. Those with an interest in vascular surgery or oncology also felt their topics to be well or reasonably well covered, but transplantation and traumatology are two areas which might benefit from increased exposure. In general, however, the original papers offered by the *Journal* were well received.

A significant finding was a desire by a quarter of the readers to have more reviews; 20 per cent of consultants, 26 per cent of senior registrars and 29 per cent of registrars made this point Eight per cent of readers would also like to see more leading articles. With an increased number of editorial pages available in the *Journal* this year it should be possible for the editors to comply with these wishes.

It is interesting to find that only 2 per cent of British readers felt there were too many papers from overseas; this was balanced by another 2 per cent who wished to see more non-British papers. In 1990 nearly half of the articles published in *The British Journal of Surgery* came from countries other than Britain Papers are selected for publication according to merit, not geographical source, and the editors have been pleased to receive an increasing number of contributions from outside Britain, and especially from the European Community as 1992 approaches. These papers from around the world have done much to make the *Journal* one of the leading international surgical publications

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Bilateral nephrectomy before transplantation: indications, surgical approach, morbidity and mortality

C. R. Darby,
D. Cranston*,
A. E. G. Raine* and
P. J. Morris*

*Nuffield Department of Surgery, John Radcliffe Hospital, Headington, Oxford OX3 9DU and *Department of Urology, Churchill Hospital, Oxford, UK*
Correspondence to:
Mr C R. Darby

Forty patients with end-stage renal failure, who had undergone simultaneous bilateral native nephrectomy before a subsequent renal transplant operation, were reviewed with particular reference to the indications and surgical approach for bilateral nephrectomy and to the complications of the procedure. The main indications for bilateral nephrectomy are hypertension resistant to medical therapy, persistent symptomatic renal infection, severe renal protein loss and occasionally polycystic kidneys or bilateral renal tumours. In this consecutive series of 40 patients both kidneys were removed because of chronic pyelonephritis with reflux (n = *28*)*, glomerulonephritis with reflux* (n = *9*) *and uncontrolled hypertension* (n = *3*)*. Surgical morbidity was less in patients who had bilateral nephrectomy performed through bilateral vertical lumbotomy incisions. There was no surgical mortality.*

In the early days of renal transplantation bilateral nephrectomy was performed frequently before transplantation, the usual indications being either infection with or without vesicoureteric reflux, or hypertension. However, as a result of the improved control of hypertension with better dialysis and drugs and the observation that recurrent episodes of infection after transplantation did not present major problems of management in most patients, bilateral nephrectomy is now performed infrequently. Furthermore, bilateral nephrectomy is usually followed by severe anaemia which commonly makes patients transfusion-dependent, which in turn might preclude transplantation due to sensitization. With the recent use of erythropoietin to prevent the anaemia of chronic renal failure and that following bilateral nephrectomy, it is possible that the indications for this procedure once again may be widened. With this in mind it was decided to review the Oxford experience of bilateral nephrectomy, looking in particular at the indications, surgical approaches, and morbidity and mortality associated with the procedure.

Patients and methods

The records of all 40 patients who underwent simultaneous bilateral nephrectomy in the Oxford unit between 1968 and 1987 were reviewed All the bilateral nephrectomies were performed on a separate occasion before renal transplantation. The records were examined retrospectively to ascertain the indications for nephrectomy, the surgical approach, and the postoperative morbidity and mortality associated with this procedure.

An anterior transperitoneal approach was used in 28 (70 per cent) patients and a bilateral vertical lumbotomy approach was used in 12 (30 per cent) patients For the lumbotomy approach the patient lies prone on the table and a vertical incision is made between the ribs above and the iliac crest below The incision is deepened through the aponeurosis which splits medially to encompass the erector spinae muscles and laterally to become the muscular abdominal wall. This incision brings the surgeon directly on to the posterior aspect of the kidney In the earlier years of this series bilateral nephrectomies performed via the bilateral lumbotomy approach were completed by removing the ureters down to the bladder via an additional Pfannenstein incision. More recently, as much ureter as possible was taken from above and the rest left *in situ*, without any ill effect All the operations were performed by a small group of experienced surgeons

Results

Forty patients underwent bilateral nephrectomy in preparation for transplantation, 25 (63 per cent) men and 15 (37 per cent) women. The indication for surgery was chronic pyelonephritis with reflux, usually with persistent infection, in 28 (70 per cent) patients, glomerulonephritis with reflux in nine (23 per cent) patients and uncontrolled hypertension in the remaining three (7 per cent).

Early complications were seen in 45 per cent of patients (*Table 1*) The severity of the infections varied, but none proved life-threatening. The incidence of chest infection after a transperitoneal approach was 39 per cent and after bilateral lumbotomy incisions was 8 per cent. The incidence of chest infection was not different between patients undergoing bilateral nephrectomy with end-stage renal failure from chronic pyelonephritis or glomerulonephritis

Wound infections occurred in three patients who had bilateral nephrectomy performed for chronic pyelonephritis Thrombosis of arteriovenous fistulae occurred after surgery in six patients. Significant postoperative bleeding was a problem in two patients who had a transperitoneal approach, but neither required re-exploration. There were no deaths in hospital or within 30 days in patients undergoing bilateral nephrectomy

Late complications were seen in three patients, all after transperitoneal incisions One patient required a laparotomy for adhesions 4 months after the bilateral nephrectomy. The other two patients developed midline incisional hernias that required repair

Discussion

One of the problems after bilateral nephrectomy is increased anaemia. In 15 of our patients, matched for disease, age, sex and graft function with 15 control patients not undergoing bilateral nephrectomy, bilateral nephrectomy resulted in a fall in mean(s d) haemoglobin concentration from 6·7(0·3) to 5·7(0·3) g/100 ml ($P<0{\cdot}001$, Student's t test). Before transplantation there was a marked difference in mean haemoglobin concentration between the nephrectomized group, 5·3(0·3) g/100 ml, and the non-nephrectomized group, 8·5(0 2) g/100 ml

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Table 1 *Early complications in 40 consecutive patients who underwent bilateral nephrectomy before transplantation*

	Surgical approach	
Complications	Transperitoneal ($n=28$)	Bilateral lumbotomy ($n=12$)
None	13 (46)	9 (75)
Chest infection	11 (39)	1 (8)
Wound infection	1 (4)	2 (17)
Postoperative bleeding	2 (7)	0
Fistula thrombosed	5 (18)	1 (8)

Values in parentheses are percentages

($P<0{\cdot}001$) Now that recombinant erthyropoietin is available it is possible to correct the anaemia associated with chronic renal failure and avoid its accentuation following bilateral nephrectomy[1,2]. This removes one of the drawbacks of the procedure, namely that the patient may become transfusion-dependent and run the risk of sensitization against human leukocyte antigen (HLA), which in turn may make subsequent transplantation difficult. However, depending on the dose and target haemoglobin concentration, the average cost per year for erythropoietin is approximately £4000 per patient and it is not widely available.

The timing of nephrectomy is important. Briggs feels that simultaneous nephrectomy and transplantation increases the risk to an unacceptable degree[3], and in a review of 134 cases by Williams *et al.* an 11 per cent mortality rate occurred both with bilateral nephrectomy in pretransplant dialysis patients and also when performed as a combined procedure with transplantation[4]. It has been the Oxford practice to perform nephrectomy at least 6–8 weeks before transplantation to allow time for full recovery without the disadvantage of anaemia. The use of erythropoeitin would allow nephrectomy to be carried out at a longer interval before transplantation, but would be expensive.

Calman *et al.* outlined three disadvantages of bilateral nephrectomy, two practical and one theoretical[5]. First, if the patient is still passing urine the loss of both kidneys increases the degree of fluid restriction required; second, there is increased likelihood of developing severe anaemia following bilateral nephrectomy; and third, there is an increased risk of renal osteodystrophy from the removal of the site of conversion of 25-hydroxycholecalciferol to 1, 25 dihydroxycholecalciferol, the active metabolite[6]. However, renal activation of cholecalciferol is already reduced in end-stage renal failure and it is unlikely that bilateral nephrectomy significantly changes the clinical situation.

Chronic pyelonephritis used to be the major indication for bilateral nephrectomy because of the presumed risk of reactivation of intrarenal infection in the immunosuppressed patient However, there is no good evidence to support this. Indeed, in the Oxford experience, no patient with chronic pyelonephritis who did not have a bilateral nephrectomy had serious problems after transplantation. Urinary infection after transplantation is usually asymptomatic and not associated with deterioration in renal function[5,7].

Polycystic kidneys have often been removed on grounds of size, loin pain, intrarenal haemorrhage or infection[5]. However, polycystic kidneys usually shrink following transplantation and removal is required only if the kidneys are massive. If size is the only indication it is usually sufficient to remove only one kidney to leave space for the graft. Polycystic kidneys may need to be removed if there is associated persistent infection or severe hypertension[3].

Anti-glomerular basement membrane antibody nephritis used to be considered an indication for nephrectomy in the expectation of accelerating the disappearance of the antibody from the blood[8]. However, it is now appreciated that such antibody is only detectable in the blood for a limited period and bilateral nephrectomy does not influence its rate of disappearance[9].

Current indications for bilateral nephrectomy are rare but include heavy proteinuria leading to gross oedema, some cases of reflux nephropathy with refractory renal parenchymal infection and bilateral renal tumours. There exist a few dialysis patients, with severe hypertension which cannot be adequately controlled by dialysis or drugs, who may respond dramatically to bilateral nephrectomy[10–14], although other workers feel that hypertension can always be controlled by haemodialysis, even in the presence of high plasma renin levels[15] Curtis *et al.* have recently re-emphasized the value of native nephrectomy as a means of controlling severe hypertension before transplantation[16].

The present data support the suggestion of others that a bilateral lumbotomy approach may carry a lower morbidity than a transperitoneal approach[17]; early or late complications occurred in 54 per cent after a transperitoneal approach compared with 25 per cent after lumbotomy. The difference between the incidence of chest infection in the transperitoneal group (39 per cent) and the lumbotomy group (8 per cent) did not reach statistical significance in this small sample size (Fisher's exact test). This reduction may be related to less postoperative pain and a decrease in abdominal distension after the bilateral lumbotomy approach. A disadvantage of the posterior approach is relatively poor access to the major renal vessels and it is suited better to small kidneys If the kidneys are very large or additional surgery such as splenectomy or peptic ulcer operation is required, then the transperitoneal route is the preferred option.

The reported mortality rate for bilateral nephrectomy varies from 10·4 per cent[4] to 0 per cent (with the use of a bilateral lumbotomy approach)[17]. The absence of any deaths in the present series is in keeping with more recent experience[17] and suggests that bilateral nephrectomy is not an unduly hazardous procedure in the hands of experienced surgeons When used appropriately for small kidneys the bilateral lumbotomy approach may decrease early complications and it is unlikely to be complicated by later wound herniation or intraperitoneal adhesions.

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Carcinoma of the rectum: a 10-year experience

A consecutive series of 303 patients with carcinoma of the rectum and distal sigmoid colon treated by a single surgeon over a 10-year period are reported. Of these, 202 underwent an anterior resection, 85 an abdominoperineal excision of the rectum and 16 a coloanal anastomosis. Surgery was considered palliative in 52 patients undergoing anterior resection and 24 undergoing abdominoperineal resection. The 30-day hospital mortality rate was six patients (3 per cent) for anterior resection and two patients (2 per cent) for abdominoperineal resection. Peroperative anastomotic testing demonstrated leakage in five stapled anastomoses; these were rectified and no clinical sequelae occurred. Two patients (1 per cent) developed a clinical anastomotic leak, one of which proved fatal; in each case the intraoperative test was negative. The overall 5-year survival rate was 64 per cent after anterior resection and 52 per cent after abdominoperineal resection; the median follow-up was 64 months. The incidence of local pelvic recurrence was 6·4 per cent after anterior resection and 14 per cent after abdominoperineal (not significant). These results confirm the success of sphincter-saving anterior resection combined with total mesorectal excision, routine full mobilization of the splenic flexure and cancercidal lavage of the distal rectum in the treatment of low rectal carcinomas; morbidity, local recurrence and survival are not compromised.

A. R. Dixon,
W. A. Maxwell and
J. Thornton Holmes

Peterborough District Hospital,
Peterborough PE3 6DA, UK
Correspondence to:
Mr A. R. Dixon, Professorial Unit
of Surgery, City Hospital,
Nottingham NG1 5PB, UK

Following the development in the 1970s of coloanal anastomoses[1] and mechanical stapling instruments[2] it became possible to restore functional gastrointestinal continuity in the majority of patients with low rectal cancer[3,4]. To be effective the benefits of anterior restorative resection must not be compromised by an increased incidence of anastomotic dehiscence or local recurrence[5,6]. In this paper a 10-year experience of 303 consecutive patients with rectal cancer is presented in whom a vigorous policy of restorative anterior resection has been applied.

Patients and methods

Three hundred and three patients with operable carcinomas of the rectum who had been electively admitted over the 10-year period to January 1988 to a single surgical unit were reviewed. Patients were only included if they had undergone radical excision of the tumour (including mesorectum and left colon): 202 patients (67 per cent) had an anterior resection; 85 (28 per cent) an abdominoperineal excision of rectum; and 16 (5 per cent) a Parks' sleeve transanal anastomosis[1]. Operative mortality was defined as death occurring at operation or in the subsequent 30 days.

The median age of patients treated by anterior resection and abdominoperineal resection was 69 years (range 31–91 years) and 65 years in the case of the coloanal anastomoses (range 45–74 years); 51 per cent of the anterior resections, 60 per cent of the abdominoperineal resections and 75 per cent of the coloanal anastomoses were performed in men. The distribution of the tumours as measured by preoperative rigid sigmoidoscopy is shown in *Table 1* (four patients had synchronous tumours identified in the operative specimen). The degree of differentiation and Dukes' classification of each tumour was recorded from the pathologist's report (*Table 2*), distal tumour clearance was not formally recorded. Surgery was considered palliative in 52 patients (26 per cent) undergoing anterior resection (17 had liver metastases, 37 clinical evidence of extensive local spread) and in 24 patients (28 per cent) having abdominoperineal excisions; six of these had both hepatic metastases and extensive local spread. Local spread was defined as that which involved the mesorectum, colonic mesentery or peritoneum and when irresectable was termed extensive. All 16 Parks' sleeve procedures were thought to be 'curative'.

Table 1 *Tumour distance from anal verge as measured by sigmoidoscopy*

Height (cm)	Anterior resection ($n=202$)*	Abdominoperineal ($n=85$)	Parks' sleeve ($n=16$)
<5	17	61	8
5–10	79	24	8
11–15	87	–	–
15–20	23	–	–
Median height (cm)	11	3·5	5

* Four patients had synchronous tumours identified in the operative specimen

Table 2 *Tumour details (Dukes' classification, grade of malignancy) and presence of synchronous polyps*

	No. of patients		
	Anterior resection ($n=202$)*	Abdominoperineal ($n=85$)	Parks' sleeve ($n=16$)
Dukes' classification			
A	21	1	3
B	93	38	7
C	75	40	6
'D'	17	6	–
Grade			
G1	49	4	4
G2	130	60	8
G3	27	21	4
Polyps			
Tubular adenomas	41	8	–
Villous adenomas	14	4	–
Tubulovillous	6	–	–

* Four patients had synchronous tumours identified in the operative specimen

Bowel preparation was by oral magnesium sulphate and Vivonex®

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(Norwich Eaton, Newcastle upon Tyne, UK) and rectal washouts. Antibiotic prophylaxis consisted of oral neomycin (1 g 6-hourly) and metronidazole (400 mg 8-hourly) in 65 per cent of patients. The remainder received peroperative intravenous cefuroxime (750 mg) and metronidazole (500 mg) repeated at 8 and 16 h. Prophylactic subcutaneous low-dose heparin had been administered to 216 patients. All surgery was conducted through a full length midline incision with the patient in the Lloyd Davies position. In the case of anterior resections the entire left colon, including splenic flexure and transverse colon, was mobilized. All patients had flush ligation of the inferior mesenteric artery close to the aorta and the inferior mesenteric vein at the inferior border of the pancreas; any palpable para-aortic lymph nodes were also removed. Sharp scissor dissection of the avascular plane between the mesorectum and the autonomic nerve plexuses in the pelvis was then performed and continued until the rectum and mesorectum could be lifted clear of the levators. The descending and sigmoid colons were then excised along with the mesorectum[7] *in toto*, using either the splenic flexure or proximal descending colon for the neorectum. In patients undergoing restorative resections, the rectum was instilled with the cancercidal agent mercury perchloride for 2 min before transection. Although not obtained on many occasions, a minimal distal margin of clearance of approximately 2 cm was attempted. Total mesorectal excision was omitted in the 17 patients with hepatic metastases.

Eighty-three anastomoses were hand sewn and 119 stapled using the 31 EEA® (Auto Suture, Ascot, UK) instrument. All the stapled anastomoses were tested for leakage of saline introduced via a rectal catheter. Following meticulous haemostasis the presacral space was drained for 72 h using a Penrose drain. In the case of the abdominoperineal resections, two suction drains were employed. A temporary covering colostomy was added in 49 patients: in all 16 Parks' procedures; in 13 low and difficult hand sewn anastomoses, in 17 routinely during early experience of stapled anastomoses; and in three patients who had a transverse colostomy added following the demonstration by saline distension of a significant intraoperative anastomotic leak. Nasogastric decompression was employed in each patient. With the advent of stapling devices, management policy changed through the 10-year period towards performing sphincter-saving operations (*Table 3*). Coloanal anastomoses were performed infrequently after 1983, exclusively in younger male patients with very low tumours where it was considered technically difficult to obtain a stapled anastomosis.

The operations were carried out by both consultant and supervised surgeons in training. After the operation all patients were clinically observed for evidence of anastomotic leakage. Sigmoidoscopy and contrast radiology were not employed routinely. The patients were followed at 3-monthly intervals for 3 years, 6-monthly for 2 years and then reviewed annually.

Statistical methods

Life table analysis was used to compare the survival and disease-free intervals for each subtype (Dukes' stage, absence or presence of local spread). The χ^2 method was applied to determine statistical differences between two[8] or more curves[9].

Results

Hospital stay ranged between 7 and 47 days (median 15 days); 32 per cent of the patients were discharged before the tenth postoperative day. Eight patients (2·6 per cent) died within 30 days of surgery, six following restorative procedures. Post-mortem examination attributed these deaths to bronchopneumonia in four cases, pulmonary emboli in two and superior mesenteric artery thrombosis in one case. The remaining postoperative death, a combination of renal failure and sepsis, followed a second-look laparotomy for anastomotic breakdown.

Table 3 *Types of operation performed during the 10-year period 1978–1988*

	Abdominoperineal (*n*=85)	Anterior resection (*n*=202)	Parks' sleeve (*n*=16)
January 1978–January 1983	51	75	11
January 1983–January 1988	34	127	5

Table 4 *Postoperative complications*

	Anterior resection	Abdominoperineal	Parks' sleeve
Urinary tract infection	24	7	2
Wound infection	13	11	–
Pneumonia	11	4	–
Deep venous thrombosis	9	1	–
Cardiac arrhythmias	7	1	–
Incisional hernias	6	1	1
Pulmonary embolus	6*	1	–
Bleeding duodenal ulcer	5	–	–
Small bowel obstruction	4	4	–
Secondary haemorrhage	2	2	–
Anastomotic disruption	2	–	2†
Infected haematoma	–	–	2†
Wound dehiscence	2	–	–
Impotence	1	2	–

* Two fatal; † the same case

Table 5 *Five-year survival rates* (%)

	Anterior resection	Abdominoperineal resection
Dukes' classification		
A	100	100 (n.s.)
B	71	66 (n.s.)
C	53	45 (n.s.)
Local spread		
Positive	48	50 (n.s.)
Negative	78	62 (n.s.)

n.s., Not significant

There was only one other clinical leak which settled with conservative treatment. Nine patients required a second operative procedure: reactionary haemorrhage in four cases, bleeding duodenal ulcer in two, wound dehiscence in two and drainage of a subphrenic abscess in one. Urological problems occurred in six patients; five required a transurethral resection for retention of urine and one required reimplantation of a sacrificed ureter. Urinary tract and wound infections were the most frequently encountered complications (*Table 4*). Long-term complications included admissions for adhesional small bowel obstruction (eight cases), incisional hernia repair (eight cases) and impotence (three cases).

Five-year survival rates relating to Dukes' classification as calculated by life table analysis are shown in *Table 5* (median follow-up was 64 months). Twelve patients (14 per cent) developed a pelvic recurrence following abdominoperineal procedures of whom three had what was thought to be a potentially curative resection. These patients then received radiotherapy; all died within 16 months. Thirteen patients (6·4 per cent) developed a local recurrence following restorative anterior resection of whom six were thought 'curative'. There has been only one case of an anastomotic recurrence occurring in an anterior resection at 18 months; this was successfully resected.

Before full-scale adoption of stapled anastomoses, 16 patients underwent a Park's coloanal anastomosis, all were thought to have had potentially curative resections. Two of these operations (12 per cent) were complicated by anastomotic disruption consequential to a combination of infected pelvic haematomata and bowel necrosis. Thirteen of these patients continue to show no signs of recurrent disease at a median follow-up of 69 months; three have developed metastatic spread from which two have died.

Discussion

Now that it has become possible to construct colorectal anastomoses as low as the dentate line[3,4] with maintenance of near normal continence[10], there can be no doubting the impact of mechanical stapling devices on current surgical practice. Despite the obvious advantages to patients[11], many surgeons remain hesitant in the full-scale adoption of sphincter-saving procedures fearing that potential cure may be compromised if both rectum and anal sphincters are not widely excised[6,12]. A further concern is that low anastomoses are prone to leakage resulting in higher rates of morbidity and mortality. The traditional abdominoperineal resection provides the 'gold standard' with which restorative procedures must continually be compared.

The overall 30-day hospital mortality rate in this series was 2·6 per cent, the causes of deaths being similar to other reported series[13–16]. When looked at individually there was no significant difference between mortality rates for restorative (3 per cent) and abdominoperineal (2 per cent) procedures, again in accordance with previous reports[13–16]. Patient selection clearly plays a major part in determining both operative morbidity and mortality. Throughout this series surgery has been consistently offered to all patients presenting with symptomatic rectal malignancy. To date only three patients have refused surgery and two have died from cardiovascular causes in the preoperative period.

One of the most serious complications after restorative resection is anastomotic breakdown: one patient in this series died from septic complications that followed such an occurrence The reported incidence of clinical leakage following stapled anastomoses lies between 3 and 19 per cent[17,18], differing rates being attributable to variations in surgical technique[19] and the zeal with which they are sought[20]. Prospectively randomized[21,22] and uncontrolled[23] trials have repeatedly shown no differences between the reliability of hand sewn and stapled anastomoses. The routine addition of a defunctioning stoma has been advocated by some[23] whilst others[24] have found no benefit and therefore consider it unnecessary We would support the latter view provided there was no concern about the integrity of the anastomoses. Thirty-three patients had stomas added in this series, 13 following low and difficult hand sewn anastomoses and 17 carried out routinely during early experience of stapling. Using peroperative saline to distend the rectum five anastomotic leaks were identified; all were rectified at the time of surgery, three requiring the addition of a defunctioning colostomy and no clinical sequelae followed. Two patients (1 per cent) with negative tests went on to develop a clinical leak, of which one was to prove fatal. Anastomotic testing was not used in hand sewn anastomoses, all of which were uncomplicated. The question as to whether peroperative testing may produce false positives and/or weaken an anastomosis would prove unethical to ascertain[25].

The low rate of clinical leakage (1 per cent) is attributed to very extensive mobilization of the left and transverse colons to ensure no tension and avoidance of anastomosing sigmoid colon. The mobilization of the greater omentum from the transverse colon facilitates its placement around the anastomoses in the pelvis. By basing the arterial supply of the distal colonic segment on the middle colic artery we believe its vascularity to be optimized. The need for meticulous haemostasis and the prevention of a pelvic haematoma is paramount[26]. Despite maintaining suction drainage for as long as possible, 13 per cent of our perineal wounds were complicated by sepsis.

Radiologically confirmed deep venous thrombosis was commoner in those patients treated by anterior resection, the majority having received heparin prophylaxis as compared with many of the abdominoperineal resections performed earlier in this series. This difference may relate to the restorative procedures having taken longer to perform.

Local recurrences are an important reflection of surgical technique in cancer treatment and produce the worst form of death for patients, producing pain, incontinence, discharge, etc. The problem of local recurrence remains contentious in that most studies are retrospective[27] and less favourable tumours are frequently assigned to abdominoperineal resections; in restorative procedures local recurrences are also readily detectable[28]. In this retrospective analysis local/pelvic recurrence was seen following 13 anterior resections (6·4 per cent), six of which had initially been thought to be potentially curative. The routine use of a cancercidal agent during the restorative operations may explain why only one patient to date has developed an anastomotic recurrence. Twelve patients (14 per cent) have developed a pelvic recurrence following an abdominoperineal resection, three of which were thought curative. Histology in these 12 patients showed that nine were Dukes' C tumours and eight poorly differentiated. The anastomotic recurrence that followed an anterior resection was successfully resected and the patient remains disease-free 48 months later Overall survival at 5 years did not differ significantly between patients treated by anterior (64 per cent) and abdominoperineal resection (52 per cent) This lack of significance was also maintained when analysed according to Dukes' classification and the presence or absence of local spread as identified histologically.

Bowel continuity was restored in a subgroup of 16 selected patients by using the abdomino-transanal technique, coupled with a defunctioning colostomy Careful selection and good fortune probably accounts for the observed absence of local recurrence in this group. The two patients who developed partial anastomotic disruptions fully recovered once pelvic sepsis resolved. Although favourable results were obtained in terms of recurrence-free interval and patient survival, we now prefer to restore intestinal continuity of all but the lowest resections by using stapler devices alone, avoiding the unnecessary morbidities associated with a colostomy and a prolonged stretching of the anal sphincters. Stapled anastomoses are quicker to complete.

In conclusion, the incidence of anastomotic leakage (1 per cent), local recurrence (6·4 per cent) and long-term results confirms the satisfactory use of the stapler device in patients with rectal cancer, particularly those requiring low resections. Intraoperative anastomotic testing is useful in demonstrating deficiencies in technique at a time when they can be rectified. The introduction of a cancercidal agent before rectal transection may reduce the likelihood of anastomotic recurrence.

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Anal endosonography in the investigation of faecal incontinence

P. J. Law, M. A. Kamm* and C. I. Bartram

Departments of Radiology and
**Medicine, St. Mark's Hospital,*
City Road, London EC1V 2PS, UK
Correspondence to:
Dr C. I. Bartram

Forty-four consecutive patients with incontinence of solid stool of traumatic or idiopathic aetiology were examined by anal endosonography and standard anorectal physiology tests. Anal endosonography showed an external anal sphincter defect in four out of 11 (36 per cent) patients with idiopathic (neurogenic) incontinence. In the remaining seven patients both parts of the sphincter were intact and a linear relationship was found between the resting anal canal pressure and the endosonographic thickness of the internal anal sphincter. Twenty-eight out of 33 (85 per cent) patients with incontinence of traumatic origin had external sphincter defects, confirmed by concentric needle electromyogram mapping in the 19 patients in whom this was performed. Eleven of these 28 (39 per cent) patients also had disruption of the internal spincter. Anal endosonography has revealed significant abnormalities in patients with faecal incontinence and has a complementary role to anorectal physiology in the routine investigation of these patients.

Anal manometry and electrophysiology have contributed significantly to our understanding of the pathophysiology of faecal incontinence[1,2]. In many patients the mechanism is thought to be neurogenic, with denervation of the striated muscles[3,4]. Structural changes in the internal sphincter have also been reported recently[5,6]. Alternatively the sphincter muscles may be damaged directly either during surgery, childbirth or anorectal trauma.

Until recently there has been no means of imaging the anal sphincters, so that actual disruption of a sphincter was determined from clinical examination, pressure studies and (in the external sphincter) by concentric electromyogram (EMG) mapping. However, with the development of anal endosonography, high resolution images of the separate sphincter muscles may be obtained[7,8]. This prospective study was designed to evaluate the additional anatomical information which this technique can provide in patients with faecal incontinence of various aetiologies.

Patients and methods

Forty-four consecutive patients with a history of incontinence of solid stool were studied. The patient details are summarized in *Table 1*. Anal manometry, electrophysiological studies and anal endosonography were performed in every patient, but only 25 of the 33 patients with traumatic incontinence had concentric needle EMG mapping of the external anal sphincter

Anal manometry

A slow pull-through technique was used with a water-filled latex balloon 4 mm in diameter connected to a pressure transducer, and the maximum canal pressures at rest (> 60 cmH_2O) and during voluntary contraction (40–160 cmH_2O) were determined.

EMG mapping

The concentric EMG needle was inserted 1–2 cm into each quadrant of the external sphincter and electrical activity was noted during rest and voluntary contraction.

Anal endosonography

All patients were examined in the left lateral position by one examiner (P J L.) using a Brüel and Kjær (Harrow, Middlesex, UK) ultrasound scanner with a 7 MHz rotating endoprobe. The lubricated probe with its water-filled plastic cone (*Figure 1*) was inserted into the rectum and then withdrawn slowly, and serial concentric images of the external and internal anal sphincters were obtained at different levels. The internal sphincter is a well defined hypoechoic ring, normally about 2–3 mm in thickness, just deep to the brighter submucosa (*Figure 2*) The external sphincter is a complex structure Its sonographic texture is similar to striated muscle elsewhere in the body and is moderately bright with a circular linear stranding[7,8]. Defects in the external anal sphincter appear as amorphous areas of varying echogenicity interrupting the normal striated pattern The presence of any such defect, the involved quadrant, as well as the integrity and maximum thickness of the internal sphincter were recorded.

Results

Four of the 11 patients with idiopathic incontinence were found to have an external anal sphincter defect. None of these patients had undergone EMG mapping of the external anal sphincter, because no defect was suspected clinically. In the seven patients with intact internal and external sphincters, low resting pressures (< 60 cmH_2O) were associated with an internal sphincter thickness of < 2 mm (*Figure 2*), and a linear relationship between the anal canal resting pressure and the internal anal sphincter thickness was established (*Figure 3*). However, it should be noted that no such correlation existed when there was a defect in the external anal sphincter.

In the 33 patients with traumatic incontinence, 28 had a defect in the external anal sphincter (*Figure 4*), which was associated with an internal anal sphincter defect (*Figure 5*) in 11 (*Table 2*). Combined defects resulted in a significantly lower

Table 1 *Details of 44 patients with faecal incontinence*

	Males	Females	Total	Mean age (years)
Idiopathic (neurogenic) incontinence	3	8	11	62 (45–78)
Obstetric trauma	0	14	14	41 (25–52)
Surgical or non-surgical trauma	11	8	19	44 (16–78)
Total	14	30	44	

Ranges are given in parentheses

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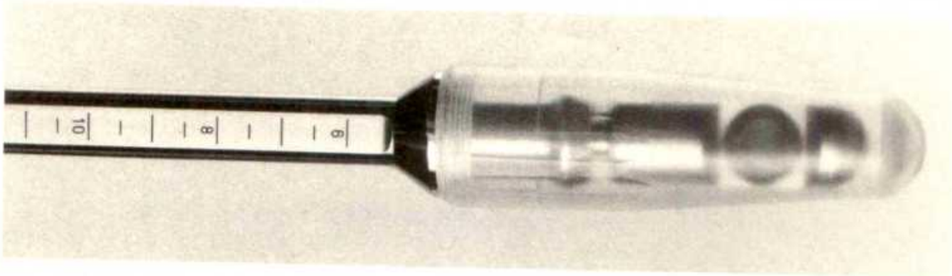

Figure 1 *The 7 MHz rotating probe protected by a plastic cone filled with degassed water for acoustic coupling*

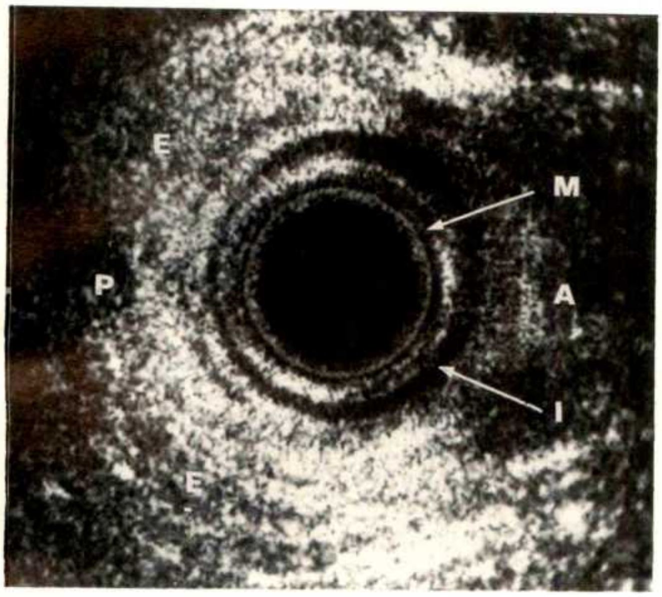

Figure 2 *Abnormally thin internal sphincter of maximum thickness 1·5 mm. The resting pressure in this incontinent patient was 40 cmH$_2$O. The image has been rotated to lie in the same plane as the patient, so that A = anterior, P = posterior. M denotes the mucosa/submucosa of the anal canal surrounding the cone of the probe. The internal sphincter (I) is well defined by a thin hypoechoic black ring. Surrounding this is the more echogenic and linear texture of the external anal sphincter (E)*

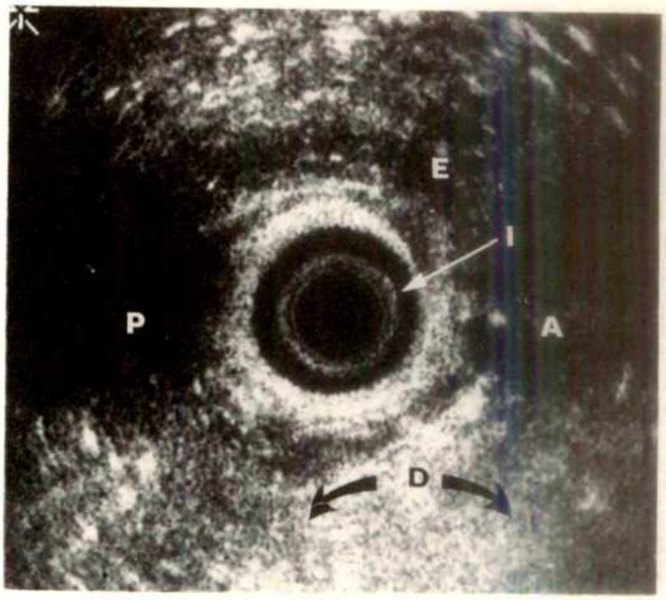

Figure 4 *External sphincter defect (D). Note the normal internal sphincter (I) and the difference in texture between the normal external sphincter (E) and the hyperechoic amorphous texture of the defect (D); A, anterior; P, posterior*

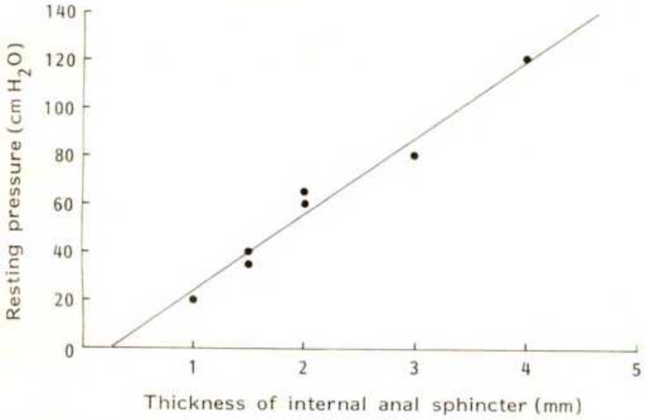

Figure 3 *Resting pressure (cmH$_2$O)* versus *internal sphincter thickness (mm) in seven patients with idiopathic incontinence and intact sphincters;* $r = 0.998$, $P < 0.00001$

resting pressure (*Table 3*). The two patients with an isolated internal anal sphincter defect had a history of a previous anal stretch procedure and were found to have a low maximum anal canal resting pressure (40 and 25 cmH$_2$O respectively) with normal voluntary squeeze pressures (140 and 100 cmH$_2$O respectively).

Twenty-five patients underwent EMG mapping and in every

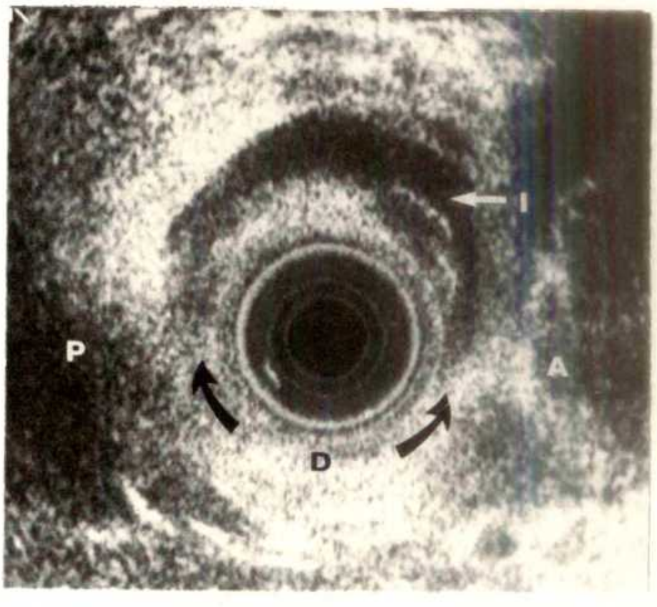

Figure 5 *Internal sphincter defect (D). The residual internal sphincter (I) has become somewhat bunched up and appears slightly thickened because of this. There is a large defect (D) in the left half of the sphincter. A, anterior; P, posterior*

Table 2 *Findings at anal endosonography in 44 patients with faecal incontinence*

	Idiopathic incontinence	Obstetric trauma	Surgical or other
Internal anal sphincter defect only	0	0	2
External anal sphincter defect only	4	10	7
Internal and external anal sphincter defect	0	4	7
No defect	7	0	3
Total	11	14	19

Table 3 *Maximum anal canal resting pressure following trauma in 28 patients with external anal sphincter defects*

	No. of patients	Resting pressure (cmH_2O)	
		Range	Mean(s.e.m.)
Internal anal sphincter			
Intact	17	20–120	55(27·9)
Damaged	11	0–60	35(3·6)

Standard error of difference between means = 2·58; $P < 0·01$

case there was agreement with anal endosonography regarding the presence (19 cases) and quadrant involved, or the absence (six cases) of a defect in the external sphincter.

Discussion

Continence of faeces depends on the integrity and function of both the internal anal sphincter and the striated muscles of the pelvic floor and anal canal[9]. High pressure within the anal canal is generated by the internal anal sphincter, which provides 85 per cent of the maximum pressure at rest[10]. The striated sphincter muscles, namely the external anal sphincter and puborectalis, display continuous tonic electromyographic activity[11]. The combined effect is to maintain apposition of the walls of the anal canal which, with accurate sensory discrimination, prevents rectal leakage in normal circumstances[12].

In this study we have demonstrated that in idiopathic (neurogenic) incontinence the maximum resting tone of the anal canal depends on the integrity of the external anal sphincter; there is close correlation between this resting pressure and the thickness of the internal anal sphincter when the external anal sphincter is intact. It has already been established that in patients with idiopathic incontinence there is atrophy and fibrosis of the internal anal sphincter[5,6]. The present study suggests that a reduction in continence and measured anal canal resting pressure may be accompanied by thinning of the internal sphincter. Most of the patients with post-traumatic faecal incontinence were found to have an external sphincter defect; however, a substantial number also had an internal anal sphincter defect. The anal canal resting pressure was significantly lower in those with loss of integrity of both components of the sphincter mechanism. The presence of an internal anal sphincter defect in 29 per cent of the patients with obstetric trauma was an unexpected finding and may be significant in surgical management.

Unconscious faecal soiling may be the result of low resting anal canal pressure. Ambulatory[13] and static[14] studies have shown that these patients have an abnormality in the frequency and duration of spontaneous internal anal sphincter relaxation, implying that the structure and behaviour of this muscle are abnormal. On the other hand if the sphincter mechanism is stressed by an urge to defaecate or a high rectal pressure, integrity of the external anal sphincter may be esssential to resist this stimulus. Urge incontinence, as opposed to passive incontinence, may therefore be the result of external anal sphincter damage.

It is therefore essential in both types of incontinence to assess the integrity of the internal and external sphincters. Anal endosonography appears to be a safe and accurate means of doing this. It can accurately delineate the site of an external anal sphincter defect[15] and is much less uncomfortable than concentric needle EMG mapping. It is the only method to assess the internal sphincter directly. The thickness of the internal sphincter would appear to be related to its function and it can easily be measured. Anal endosonography has a complementary role to anorectal physiology studies and is important in delineating sphincter damage in patients with incontinence.

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Ultrasonography in the diagnosis of acute appendicitis

Ultrasonography with graded compression was performed in 525 patients with clinical signs of acute appendicitis. Of 207 patients with surgically proven appendicitis the inflamed appendix (diameter ≥6 mm) had been visualized sonographically in 177 (86 per cent). The score for non-perforated appendicitis (91 per cent) was higher than for perforated appendicitis (55 per cent). Twenty-four patients in whom an inflamed appendix was seen on ultrasonography did not undergo surgery because of rapidly subsiding symptoms ('abortive appendicitis'). Four of these 24 developed recurrent appendicitis warranting surgery. Two underwent elective appendicectomy and 18 have remained symptom-free. Of 155 patients with a subsequently confirmed alternative condition, ultrasonography made the correct diagnosis in 140: bacterial ileocaecitis (69), mesenteric lymphadenitis (eight), gynaecological conditions (34), urological conditions (eight), caecal diverticulitis (six), perforated peptic ulcer (six), Crohn's disease (two) and miscellaneous conditions (seven). Of 139 patients in whom no definite diagnosis was made ultrasonography showed no abnormalities in 138. In four patients a false positive sonographic diagnosis of appendicitis was made and in two patients with appendicitis an alternative condition was incorrectly diagnosed. During the last 3 years of the study the negative appendicectomy rate was 7 per cent and delay beyond 6 h after admission occurred in only 2 per cent of patients with surgically proven appendicitis. When used to complement the clinical diagnosis ultrasonography improves the diagnostic accuracy and patient management in those suspected of having acute appendicitis.

H. W. A. Ooms,
R. K. J. Koumans*,
P. J. Ho Kang You* and
J. B. C. M. Puylaert

Departments of Radiology and
**Surgery, Westeinde Hospital,*
Lijnbaan 32, 2512 VA, The Hague,
The Netherlands

Correspondence to:
Dr J. B. C. M. Puylaert

Appendicitis is still the most common reason for acute abdominal surgery in the Western world. The diagnosis may be wrongly made or initially overlooked. The first error leads to an unnecessary operation and the second to delay. The 'negative appendicectomy' rate ranges from 22 to 28 per cent[1–5] and postadmission delay for more than 6 h due to diagnostic uncertainty occurs in 20–28 per cent[5,6].

Ultrasonography using the graded compression method markedly enhances diagnostic accuracy and following an initial study[7] comparable results have been obtained by others[8–10] and the clinical significance of the procedure has been emphasized[11–13].

In this study experience with diagnostic ultrasonography in 525 patients with suspected acute appendicitis is analysed and we discuss its applications and limitations.

Patients and methods

Between 1985 and 1989 525 patients with clinical signs of acute appendicitis were examined by ultrasonography. There were 225 male and 300 female patients, with an average age of 28·0 years (range 4–85 years).

This was not a consecutive group because a number of patients (usually young men) with typical signs of acute appendicitis underwent appendicectomy without preceding ultrasound examination. Patients with clinical signs of an appendiceal mass warranting conservative management or abscess drainage were excluded from the study. The examinations were performed by a radiologist trained in ultrasonography using the Aloka SSD 280 LS (Aloka Co, Tokyo, Japan) with T-shaped 5 and 7·5 MHz linear array transducers with side-view capacity.

Examination of the right lower abdomen was performed with graded compression[7] in which intervening fat and bowel were displaced and/or compressed thereby eliminating disturbing artefacts from bowel contents and reducing the distance from the transducer to the appendix, allowing the use of a high frequency transducer with a satisfactory image quality. The transducer was handled in a gentle palpating manner to avoid pain. If the compression was exerted gradually with care the examination was well tolerated.

If the appendix was visualized and its diameter (from the periphery of the muscularis to the opposite side) was ≥6 mm it was considered to be inflamed (*Figure 1*).

If an alternative condition, thought to be responsible for the patient's symptoms, was diagnosed by ultrasonography, this was recorded. In the later part of the study the location of the inflamed appendix was marked with a skin pencil. This occasionally influenced the most appropriate incision. In all patients with appendicitis the time interval between admission and subsequent operation was noted. The final diagnosis was established by laparotomy (surgical and histological findings), laparoscopy or clinical grounds, supported by sonographic follow-up and frequently by computed tomography, conventional radiological studies, endoscopy, bacteriological tests, etc. The ultimate criterion for acute appendicitis was the histological demonstration of polymorphonuclear leucocytes throughout the thickness of the appendix wall. Criteria for a perforation was a hole in the appendix and/or the presence of pus or faeces in the peritoneal cavity.

Results

Results comparing ultrasonography and final clinical diagnosis are shown in *Table 1*. The standard of reference for the final diagnosis was laparotomy in 265 patients, laparoscopy in 26 patients and other methods described above in 234 patients.

The final diagnosis was appendicitis in 231 patients, an alternative condition in 155 and non-specific abdominal pain in 139.

Appendicitis

In 231 patients the final diagnosis was acute appendicitis: non-perforated appendicitis in 160, perforated appendicitis in

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Table 1 *Overall results with regard to final diagnosis and ultrasonography findings in 525 patients with clinical signs of acute appendicitis*

		Ultrasonography results		
Final diagnosis	No. of patients	Positive for appendicitis	Positive for an alternative condition	Non-diagnostic or normal
Acute, non-perforated appendicitis	160	145	1	14
Acute, perforated appendicitis	33	18	1	14
'Abortive' appendicitis	38	38	–	–
Bacterial ileocaecitis	69	–	69	–
Mesenteric lymphadenitis	8	–	8	–
Gynaecological conditions (ovarian cyst 24, ectopic pregnancy 6, salpingitis 9, adnexal torsion 4, postpuerperal endometritis 1)	44	–	34	10
Urological conditions (ureterolithiasis 5, pyelonephritis 3, pelviureteric obstruction 1)	9	–	8	1
Perforated peptic ulcer	8	2	6	–
Caecal diverticulitis	6	–	6	–
Crohn's disease	2	–	2	–
Miscellaneous conditions (cholecystitis 1, eosinophilic enteritis 1, primary pneumococcal peritonitis 1, ampullary carcinoma 1, small bowel obstruction 1, incarcerated hernia 1, CAPD-peritonitis 1, rectus haematoma 1, sigmoid diverticulitis 1)	9	1	7	1
Non-specific abdominal pain	139	1	–	138
Total	525	205	142	178

CAPD, chronic ambulant peritoneal dialysis

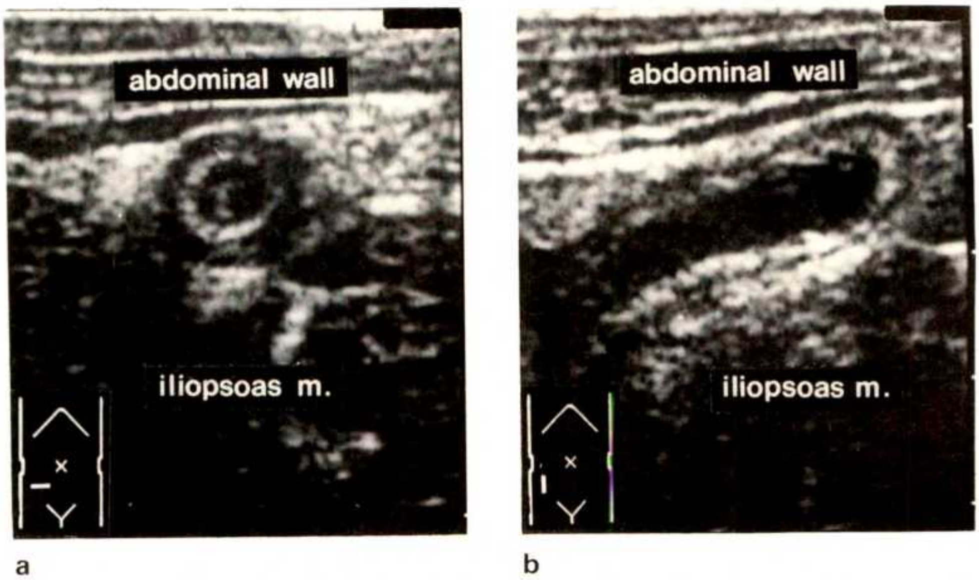

Figure 1 *Ultrasonographic image of an inflamed appendix during graded compression. The appendix is identified compressed between the abdominal wall and iliopsoas muscle.* **a** *Axial section of the appendix, clearly showing its concentrically layered structure. Its alternately hyperechoic and hypoechoic rings represent (from inside out): mucosal surface outlining the collapsed lumen; lamina propria; submucosa; muscularis; and the serosa, merging with the surrounding fatty tissue. The diameter is 10 mm.* **b** *Longitudinal section shows the tubular nature of the appendix and its blind end*

33 and 'abortive' appendicitis in 38 patients. The inflamed appendix (mean diameter 8·5 mm, range 6–14 mm) was sonographically visualized in 145 of the 160 patients (91 per cent) with non-perforated appendicitis and in 18 of 33 (55 per cent) patients with perforated appendicitis. In two patients mesenteric lymphadenitis and caecal diverticulitis were incorrectly diagnosed while in 28 patients the ultrasound examination was normal or non-diagnostic.

In 38 patients with a sonographically inflamed appendix (mean diameter 7·5 mm, range 6–11 mm) the clinical symptoms subsided within a few hours (abortive appendicitis). At the time of the ultrasound examination the appendiceal area had lost its tenderness on pressure (negative sonographic McBurney sign[7]). Despite this clinical course 14 patients underwent immediate surgery, eight because of the convincing ultrasound findings and six because of a history of recurrent attacks. The appendix was acutely inflamed in all 14. The remaining 24 patients did not undergo surgery and recovered rapidly. Follow-up ultrasound examination showed a gradual decrease in size of the appendix, which eventually became undetectable.

decrease in size of the appendix, which eventually became undetectable. Two patients underwent elective appendicectomy: at peroperative inspection and at histological examination the appendix was normal in both. Of the remaining 22 patients only four had recurrent symptoms: after 2, 7, 14 and 16 months. In all four the inflamed appendix was again detected on sonography and subsequent appendicectomy revealed acute inflammation. The other 18 patients have remained symptom-free (follow-up period 6–54 months).

Alternative conditions

Of 155 patients with a confirmed alternative condition, ultrasonography made the correct diagnosis in 140, showed no abnormalities in 12 and made a false positive diagnosis of appendicitis in three patients: two with perforated peptic ulcer and one with primary pneumococcal peritonitis (*Table 1*).

Non-specific abdominal pain

In 139 patients no definite diagnosis was made. In 138 ultrasonography showed no abnormalities and in one patient ultrasonography made a false positive diagnosis of appendicitis.

Clinical significance

The negative appendicectomy rate decreased from 32 per cent in 1985 to 12 per cent in 1986 and 7 per cent in the period from 1987 to 1989. Delay (beyond 6 h) due to diagnostic uncertainty occurred in 11 per cent of patients with surgically proven acute appendicitis in 1985, in 4 per cent in 1986 and in 2 per cent in the period from 1987 to 1989.

Discussion

The overall score for sonographic visualization of the inflamed appendix in patients with surgically proven appendicitis in this study was 86 per cent, a rate that is comparable with scores of 79–90 per cent obtained in other studies[8–12].

The rate for perforated appendicitis (55 per cent) was low compared with the rate for non-perforated appendicitis (91 per cent). This was probably due to the associated severe peritonitis which impedes adequate compression because of reflex rigidity and causes adynamic ileus with dilated bowel loops hiding the appendix from view. Fortunately in most of these patients the clinical indication for laparotomy was obvious.

A retrocaecal position of the appendix did not cause diagnostic problems because the caecum was often spastic and could be used as an acoustic window. In other cases the appendix could be demonstrated by scanning laterally. A pelvic position made sonographic demonstration occasionally impossible.

If ultrasonography demonstrates no abnormality or is not diagnostic there is still a 16 per cent (28 of 178) chance of appendicitis. When ultrasonography indicates an alternative condition the chance of appendicitis decreases to 1 per cent (2 of 142) (*Table 1*).

Appendicitis running an abortive course is a known clinical phenomenon. Of the 38 patients with abortive appendicitis, 22 did not undergo surgery and of these four patients had recurrent appendicitis. The remaining 18 patients have not had recurrent attacks within a follow-up period of 6–54 months.

Although based on preliminary results, it seems reasonable to entertain a 'wait and see' policy in patients with abortive appendicitis who do not recall similar attacks in the past and who do not plan a prolonged stay in areas without access to adequate medical care These patients should be advised to seek surgical help without delay in case of recurrent symptoms

By far the most frequent alternative condition detected on ultrasonography was bacterial ileocaecitis caused by *Yersinia*, *Campylobacter* or *Salmonella* in which the predominant symptom was right lower abdominal pain; diarrhoea was usually mild or absent. Sonographic features are characteristic and consist of mural thickening of the ileum and caecum with enlarged mesenteric lymph nodes Clinical features, sonographic diagnosis and bacteriological results have recently been described[14–16].

Mesenteric lymphadenitis was the sole finding in eight patients, predominantly children. A causative agent (rotavirus) was identified in only one. A false positive diagnosis of lymphadenitis was made in a patient with appendicitis in whom the associated moderately enlarged mesenteric lymph nodes were seen, but the inflamed appendix was overlooked.

In three female patients ultrasonography detected a specific gynaecological condition (torsion of a large dermoid cyst, rupture of a dermoid cyst and ectopic pregnancy, in which the fetus showed visible heartbeat). In a further 31 female patients visualization of adnexal abnormalities correctly suggested the gynaecological nature of the right lower abdominal symptoms.

Ultrasonography proved to be of use in patients with an ovarian cyst, adnexal torsion and ectopic pregnancy, but was of limited value in salpingitis.

In eight of nine patients with subsequently established urological disease, ultrasonography indicated the correct diagnosis: ureterolithiasis in five, pyelonephritis in two and pelviureteric obstruction in one

Caecal diverticulitis has fairly typical sonographic features[17,18] and was correctly diagnosed in all six patients with this condition. In one patient with perforated appendicitis, the base of the appendix containing a faecalith was considered to represent an inflamed caecal diverticulum and a false positive diagnosis of caecal diverticulitis was made.

Perforated peptic ulcer may cause clinical signs of appendicitis when gastric contents descend along the right paracolic gutter. This local chemical peritonitis may also cause thickening of the appendix and in two patients early in the study this led to a false positive diagnosis of appendicitis. In six other patients with perforated peptic ulcer the correct diagnosis was made as ultrasonography detected free air In four of these six patients a concomitant thickened appendix (mean diameter 7·5 mm, range 6–9 mm) was seen on ultrasonography.

In two patients with acute Crohn's disease ultrasonography suggested the correct diagnosis demonstrating a markedly abnormal terminal ileum, in one patient accompanied by prestenotic dilatation.

In five patients with small bowel obstruction, cholecystitis, incarcerated hernia, rectus haematoma and sigmoid diverticulitis, ultrasonography established the correct specific diagnosis. In one patient with ampullary carcinoma and one with eosinophilic enteritis, ultrasonography suggested the presence of an alternative condition by demonstrating dilated bile ducts and diffuse mural thickening of multiple small bowel loops.

In one patient with a primary pneumococcal peritonitis associated with liver cirrhosis, the appendix was reactively thickened (diameter 6 mm) and falsely interpreted as inflamed.

Of the 139 patients with non-specific abdominal pain, ultrasonography revealed no abnormality in 138 patients In one patient, early in the study, a thickened appendix (diameter 6 mm) was visualized, but subsequent appendicectomy revealed a normal appendix. Ultrasonographic visualization of the normal appendix was possible in only seven patients, all very slim individuals The normal appendix presented as a tubular, mobile, well compressible structure with a diameter ≤5 mm None of these seven patients was operated on. Experience in other slim individuals (healthy volunteers and patients referred for upper abdominal symptoms) confirms these criteria

The decrease in the negative appendicectomy rate to 7 per cent with a concomitant decrease in postadmission delay proves the useful role of ultrasonography in the diagnosis of appendicitis. In the group of young female patients in our study (15–45 years) the negative appendicectomy rate, traditionally as high as 35–45 per cent, was reduced to 6 per cent It should be emphasized that ultrasonography does not replace the clinical diagnosis, but complements it. Clinical diagnosis is especially crucial in those patients in whom ultrasound examination shows no abnormality or is non-diagnostic, for example the poor sensitivity of ultrasonography in perforated appendicitis. Obvious sonographic findings should still be interpreted within the clinical context, as for example in patients with abortive appendicitis.

Results of ultrasound examinations are strongly operator-dependent and require dedication and experience. Ultrasonography with graded compression enhances diagnostic accuracy and can be of great benefit to the patient.

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Primary repair of colon injuries in a developing country

V. Naraynsingh, D. Ariyanayagam and S. Pooran

Department of Surgery, General Hospital, Port of Spain, Trinidad, West Indies

Correspondence to:
Mr V Naraynsingh

Because there are several specific disadvantages to a colostomy in a developing country, primary repair for colon injury was electively performed. Sixty-one consecutive patients with colon injury were seen between 1978 and 1989 and 57 of these (93 per cent) underwent primary repair. In four a colostomy was constructed. Emergency repair was carried out regardless of site or mode of injury, presence of hypotension or peritoneal contamination. There was one death unrelated to anastomotic complications and one anastomotic leakage. The faecal fistula closed spontaneously in 4 weeks. The wound infection rate was 10 per cent. These data support the emerging view that primary repair of colon injury is the management of choice.

The traditional management of colon injury has been the formation of a colostomy. This policy is based on World War II experience and has continued unchallenged until the early 1980s[1,2]. In the past decade, however, there has been a move toward primary repair without colostomy[3,4]. The safety of this practice has been attested by several authors[4–8].

In surgical practice in a developing country, colostomy construction has obvious disadvantages. Colostomies are ill-managed by the patient due to poor education, the unreliable supply of collecting appliances and inadequate toilet facilities. Members of a largely outdoor population become social recluses and productive members of society are kept away from the workplace for prolonged periods of time.

Before the new policy of primary repair the average time from injury to colostomy closure was 14 months (because of shortage of operating theatre time). The cost to the health system is an underestimated factor; multiple admissions increase bed occupancy, operating theatre time, drug consumption and usage of manpower resources.

Since 1978, we have adopted the practice of one-stage surgery as a routine in the management of colon injury.

Patients and methods

Between 1978 and 1989, 61 patients with colonic trauma were seen. Stab wounds accounted for 28, gunshot wounds for 22, there were three cases of blunt injury and eight were iatrogenic. Of these 61 patients, 57 (93 per cent) underwent primary repair without colostomy. In four patients a colostomy was constructed; in three the injury was in the depths of the pelvis and primary repair was considered technically difficult and unsafe. The fourth case had blunt trauma to the transverse colon with much bruising of the bowel wall and a large hematoma in the mesocolon.

For primary repair the injured bowel wall was repaired using an inverting two-layer technique with 2/0 chromic catgut Neither intraoperative colonic irrigation nor peritoneal lavage was used Debridement of the bowel edges was unnecessary in most cases. In all instances perioperative broad-spectrum antibiotics were used.

Results

There was one death and one anastomotic leakage. Death occurred in a 35-year-old man with gunshot injury to the right colon, right ureter, vena cava and small intestine. These structures were repaired primarily but he remained in shock and unconscious until death 5 days later. At post mortem there was no evidence of anastomotic leakage or intraperitoneal sepsis.

Anastomotic leakage occurred in a 30-year-old man with gunshot injury to the rectosigmoid area. Debridement of the injured area was carried out before repair and, because of widespread contamination and pelvic haematoma, a drain was left near the anastomosis. He developed a faecal fistula which closed spontaneously after 4 weeks.

The overall incidence of superficial wound infection was 10 per cent (six cases) and no deep wound disruption or intra-abdominal abscess occurred

Discussion

The reduced severity of injuries in a civilian setting and advances in resuscitation and antibiotic therapy have allowed surgeons in the past decade to perform primary repair in colon injury with minimal morbidity and mortality[4–9]. In this series, the mode or site of injury, the presence of hypotension or peritoneal contamination did not influence the decision to repair the colon primarily, resulting in one of the highest rates of primary repair (93 per cent) reported in the literature.

A great deal of attention has been given in the past to so-called 'risk factors'[4,10–12], the presence of which preclude[5] primary repair of the traumatized colon. Cases for primary repair were carefully chosen and the procedure selectively practised[3,4,13]

As confidence grew in the safety of the procedure, the number of identified risk factors became smaller and the rate of primary repair increased from 52 per cent to 64 per cent[4,7]. A recent series[9] reinforces the lack of credence given to excluding cases for primary repair based on previously identified risk factors and reports a 93 per cent rate of primary repair, with only one suture line failure in 95 cases.

Peritoneal lavage is a procedure currently enjoying widespread popularity in surgical practice. In none of the cases reported in this series has this been done and our overall rate of septic complications was 10 per cent – well within the accepted margins for a contaminated procedure. A recent critical review of the literature[14] fails to support the benefit of intraoperative peritoneal lavage and our results substantiate this.

The adoption of primary repair of colon injuries was dictated by the special needs of the West Indian population and the limited resources of the health system. These results demonstrate its safety and benefits and this practice is recommended as the treatment of choice in the management of colon trauma.

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Biliary bile acid profiles in familial adenomatous polyposis

A. D. Spigelman,
R. W. Owen*,
M. J. Hill* and
R. K. S. Phillips

*St. Mark's Hospital, London and The Professorial Surgical Unit, St. Bartholomew's Hospital, London, and the *Public Health Laboratory Service, Centre for Applied Bacterial Metabolism and Research, Division of Pathology, Bacterial Metabolism Group, Porton Down, Salisbury, Wiltshire, UK*

Correspondence to:
Mr R. K. S. Phillips, St Mark's Hospital, City Road, London EC1V 2PS, UK

Patients with familial adenomatous polyposis have an excess risk for adenomas and cancers of the upper and lower gastrointestinal tract. In the upper intestine these lesions occur mainly around the ampulla of Vater and they parallel mucosal exposure to bile. In view of this finding and of evidence that bile acids play a role in colorectal carcinogenesis, biliary bile acid profiles were determined in 29 patients with familial adenomatous polyposis (12 before colectomy, 17 after colectomy) and in 28 patients without familial adenomatous polyposis (all with colons in situ). *Patients with familial adenomatous polyposis had a higher total biliary bile acid concentration than the others. The bile of patients with polyposis had a greater proportion of chenodeoxycholic acid and a lower proportion of deoxycholic acid than did the bile of patients without polyposis. The ratio of chenodeoxycholic acid and its metabolite lithocholic acid to cholic acid and its metabolite deoxycholic acid, which is related to subsequent bile acid profiles in the colon, was higher in patients with polyposis. Because bile acids influence cellular proliferation, these findings may be of importance with respect to intestinal adenoma and cancer growth.*

Patients with familial adenomatous polyposis inevitably develop large bowel cancer (unless colectomy is performed) and they are at high risk of periampullary duodenal cancer[1]. Duodenal adenomas are found in almost all of these patients, whereas adenomas rarely occur in the stomach. Within the duodenum adenomas tend to cluster around the ampulla of Vater[2]. This distribution suggests that bile may play a role in tumour growth.

It has been proposed that bile acids are important in colorectal carcinogenesis because they exert deleterious effects on cell function by increasing cellular proliferation[3,4] and by damaging cell integrity[5] and cellular genetic material[6,7]. Bile acid receptors have been demonstrated in tumour tissue[8] but their role in tumour growth is unclear[9]. Furthermore, some studies of faecal[10,11] and biliary[12,13] bile acids have shown abnormal profiles in patients at high risk of large bowel adenomas and cancers (or with a past history of these lesions), although other studies have failed to confirm these findings[14–16]. Methodological inadequacy has been advanced as a possible reason for the conflicting results of faecal bile acid studies[17].

To determine whether the occurrence and distribution of upper gastrointestinal adenomas in patients with familial adenomatous polyposis is associated with abnormal bile acid profiles, we collected and tested bile samples from patients with polyposis, the majority of whom had proven duodenal adenomas, and from control patients.

Patients and methods

Bile collection

Ethical Committee approval was obtained for methods of bile sampling. All bile was snap-frozen in liquid nitrogen and stored at −70°C. A history of antibiotic use was taken from all patients.

Gallbladder bile

This was collected at the start of laparotomy from the normal gallbladders (as determined by palpation before and after aspiration) of 12 patients with familial adenomatous polyposis undergoing colectomy (five men and seven women of median age 35·5 years, interquartile range 25–43 years). Metronidazole and gentamicin were given only peroperatively.

There were 13 control patients (five men and eight women of median age 50 years, interquartile range 41–62 years) comprising seven patients undergoing elective cholecystectomy for gallstones (one man and six women of median age 61 years, interquartile range 41–67 years) to whom antibiotics were given only peroperatively, five previously healthy beating heart organ donors and one laparotomy patient, all without gallstones (four men and two women of median age 45·5 years, interquartile range 28–62 years). None of these patients had been receiving total parenteral nutrition, although three organ donors had been given antibiotics (two on benzyl penicillin and flucloxacillin and one on metronidazole) for between 1 and 3 days.

Patients were fasted for a mean of 9 h before sampling, except for the beating heart donors who had been fasted for a mean of 3 days (range 1–5 days).

Duodenal bile

This was collected at upper gastrointestinal endoscopy following the intravenous injection of 5 μg of the cholecystokinetic agent ceruletide (Farmitalia Carlo Erba Ltd., St. Albans, Hertfordshire, UK). Patients with a history of gallstones (prior cholecystectomy or radiologically proven stones) or of recent antibiotic use were excluded.

The familial adenomatous polyposis group comprised 17 patients (13 men and four women of median age 43 years, interquartile range 40–50 years), all of whom had undergone colectomy, 14 with ileorectal anastomosis and three with ileostomy. All but three of these patients had duodenal polyps, and one of the patients with an apparently normal duodenum had a microscopic adenoma at the papilla of Vater. The control group consisted of 15 patients (ten men and five women of median age 38 years, interquartile range 28–58 years) who were being investigated for possible peptic ulceration.

Bile analysis

All samples were analysed in coded form by R.W.O. and M.J.H., the code being broken at the completion of the study.

Ethanol (20 ml) was added to a stoppered flask containing a 1 ml aliquot of bile and was left to stand at 37°C for 17 h. The samples were centrifuged for 15 min and the supernatant was removed. This process was repeated twice with a further 20 ml ethanol and the pooled supernatants were evaporated to dryness by flash evaporation. The residue was resuspended in 20 ml methanol and dried down under a stream of nitrogen.

The samples were analysed using high performance liquid chromatography as previously described[18,19] and the results were checked by thin layer chromatography and by gas–liquid chromatography. Analyses were performed using Waters equipment (Waters Ass., Milford, MA, USA) and the column was a Nova-pak reverse phase cartridge (inner diameter 100 × 8 mm) compressed in a Waters RCM-100 module. The mobile phase consisted of methanol dihydrogen

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potassium phosphate (3:1, v/v) at pH 5·5 and was filtered and degassed before use. A flow rate of 0·7 ml/min was used during the analysis and a variable wavelength Lamda-Max 481 LC spectrophotometer set at 205 nm was used for detection

The dry extract was dissolved in 9 ml mobile phase, and 1 ml dexamethasone solution (1 mg/ml in mobile phase) was added as an internal standard. All samples were filtered before analysis Bile acid amidates were identified by reference to known standards and were quantified relative to the internal standard using a Waters 740 data module as an integrator, with relevant corrections for detector response to the individual bile acid amidates. Detector response for each bile acid amidate was shown to be linear (range 0·05–1·0 mg/ml).

Statistics

All results are expressed as the median value with the interquartile range as the index of dispersion. Significance testing was by the Mann–Whitney *U* test (two tailed).

Results

Gallbladder bile

The bile acid profiles found in the gallbladder bile of patients with and without familial adenomatous polyposis are shown in *Table 1*. The bile of patients with polyposis contained significantly more total bile acid amidates (TBAA), 91 *versus* 64 mg/ml ($P=0{\cdot}05$), than did control bile, and this trend was maintained when patients with gallstones (seven controls) were excluded, 91 *versus* 51 mg/ml ($P=0{\cdot}02$).

The proportion of amidated chenodeoxycholic acid (CDCA) was significantly higher, 46 *versus* 35 per cent ($P<0{\cdot}001$), and that of amidated deoxycholic acid (DCA) was significantly lower, 8 *versus* 23 per cent ($P<0{\cdot}01$), in polyposis bile compared with control bile (*Figures 1a* and *2a*), so that the proportion of amidated primary bile acids (PBA) was significantly higher, 92 *versus* 75 per cent ($P<0{\cdot}01$), and that of amidated secondary bile acids (SBA) was lower, 8 *versus* 25 per cent ($P<0{\cdot}01$) in polyposis bile. The ratio of CDCA plus lithocholic acid (LCA) to cholic acid (CA) plus DCA was higher in the bile of patients with polyposis, 0·886 *versus* 0·606 ($P=0{\cdot}0024$). These differences retained statistical significance when the group of patients with gallstones ($n=7$) was excluded.

When more precise age-matching was used the same differences were observed for TBAA, CDCA, DCA, PBA, SBA and the CDCA+LCA:CA+DCA ratio, but statistical significance was lost, perhaps because of smaller numbers ($n=6$ for each group; *Figures 1b* and *2b*).

Duodenal bile

The bile acid profiles found in the duodenal bile of patients with familial adenomatous polyposis (the group of patients who had undergone colectomy) and in the duodenal bile of the controls without polyposis are shown in *Table 2*. The same differences in bile acids were detected here as were found in the gallbladder bile samples. Statistical significance was retained between patients with and without polyposis, respectively, for differences in DCA, 1 *versus* 13 per cent ($P<0{\cdot}01$); PBA, 99 *versus* 86 per cent ($P<0{\cdot}005$); and SBA, 1 *versus* 14 per cent

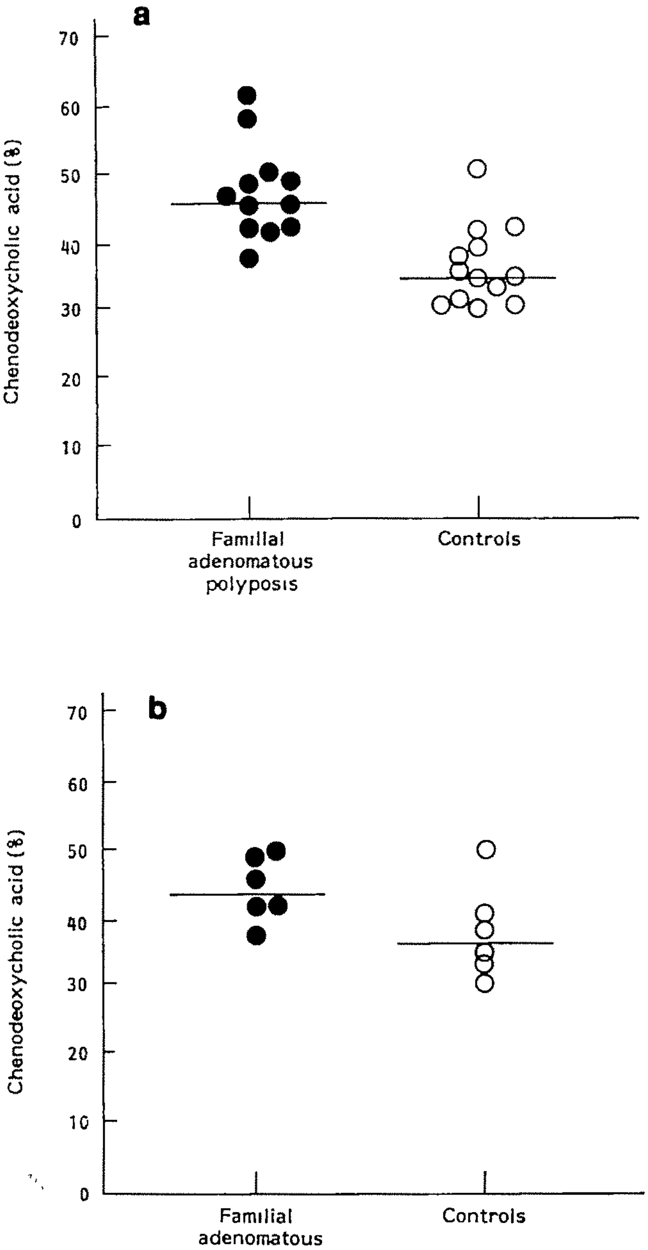

Figure 1 **a** *Chenodeoxycholic acid levels in gallbladder bile were significantly different between non-age-matched patients with familial adenomatous polyposis and controls* ($P<0{\cdot}001$). *The median ages (and interquartile ranges) were, respectively, 35·5 (25–43) years and 50 (41–62) years* ($P<0{\cdot}05$) *Statistical significance was retained after exclusion of patients with gallstones* ($P=0{\cdot}0182$). **b** *Age-matching removed significance because of smaller numbers, but the trend remained the same* ($P=0{\cdot}132$) *Horizontal bars denote median values*

Table 1 *Gallbladder bile acid profiles in patients with familial adenomatous polyposis and controls*

	Age (years)	TBAA (mg/ml)	Amidates as a percentage of TBAA							
			CA	CDCA	DCA	LCA	PBA	SBA	G	T
Familial adenomatous polyposis ($n=12$)	35·5 (25–43)	91 (77–141)	43 (36–46)	46 (42–50)	8 (7–12)	0.4 (0–0·6)	92 (87–92)	8 (8–13)	70·5 (61–81)	29·5 (19–39)
Controls ($n=13$)	50 (41–62)	64 (41–94)	38 (31–52)	35 (31–41)	23 (14–31)	0 (0–1·2)	75 (70–86)	25 (14–30)	73 (59–76)	27 (24–41)
*P**	<0·05	<0·05		<0·001	<0·01		<0·01	<0·01		

Values are medians with interquartile ranges in parentheses. TBAA, total bile acid amidates. CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; PBA, primary bile acids, SBA, secondary bile acids; G, glycine conjugates; T, taurine conjugates. * $P>0{\cdot}05$ unless stated otherwise

($P<0{\cdot}005$). Significance was gained for CA, 49 *versus* 40 per cent ($P<0{\cdot}01$), but statistical significance was lost for differences in the TBAA concentration, 11·9 *versus* 10·2 mg/ml ($P=0{\cdot}3501$), for the proportion of CDCA, 45 *versus* 43 per cent ($P>0{\cdot}05<0{\cdot}7$); and for the ratio of CDCA + LCA:CA + DCA, 0·854 *versus* 0·668 ($P=0{\cdot}6548$). Taurine bile acid conjugates were significantly lower than glycine bile acid conjugates in polyposis bile, 22 *versus* 27 per cent ($P<0{\cdot}05$), reversing the trend found in gallbladder bile (*Table 1*).

Gallbladder and duodenal bile

The difference in TBAA concentration found between samples obtained from the gallbladder and those from bile-rich duodenal fluid is a dilution effect. Results for individual bile acids are therefore expressed as a percentage of TBAA to minimize this effect.

Statistically significant differences between the two polyposis groups (*Tables 1* and *2*) were lower proportions of CA, 43 *versus* 49 per cent ($P<0{\cdot}05$), and higher proportions of the secondary bile acids DCA, 8 *versus* 1 per cent ($P<0{\cdot}05$), and LCA, 0·4 *versus* 0 per cent ($P<0{\cdot}05$), and thus of SBA overall, 8 *versus* 1 per cent ($P<0{\cdot}05$) in the precolectomy group. The proportion of PBA was consequently higher in the postcolectomy group, 99 *versus* 92 per cent ($P<0{\cdot}05$).

There were no significant differences (apart from the TBAA concentration referred to above) between the two control groups. Comparison between the gallbladder bile of patients with polyposis who had an intact colon ($n=12$) and the duodenal bile of patients without polyposis, who all had an intact colon ($n=15$), revealed that the percentage of DCA was lower in the patients with polyposis (8 per cent) than in controls (13 per cent), but this was not statistically significant ($P=0{\cdot}18$). Similarly, although both the percentage of CDCA (46 *versus* 43 per cent) and the CDCA + LCA:CA + DCA ratio (0·89 *versus* 0·67) were higher in the polyposis population compared with controls, neither of these differences was statistically significant ($P=0{\cdot}3$).

Discussion

This study was conducted because of the observed distribution of upper gastrointestinal polyposis in areas maximally exposed to bile and because of the markedly increased risk of periampullary cancer in patients with familial adenomatous polyposis. Patients with polyposis are, of course, also at very high risk for colorectal cancer, where bile acid abnormalities might also be relevant.

We have found that total bile acids, particularly the primary bile acids (CDCA before colectomy, CA after colectomy), occur in higher concentrations in patients with familial adenomatous polyposis and that the secondary bile acid, DCA, occurs in a lower concentration. This means that there are differences in the ratios of primary and secondary bile acids.

The relevance of the bile acids in intestinal neoplasia has

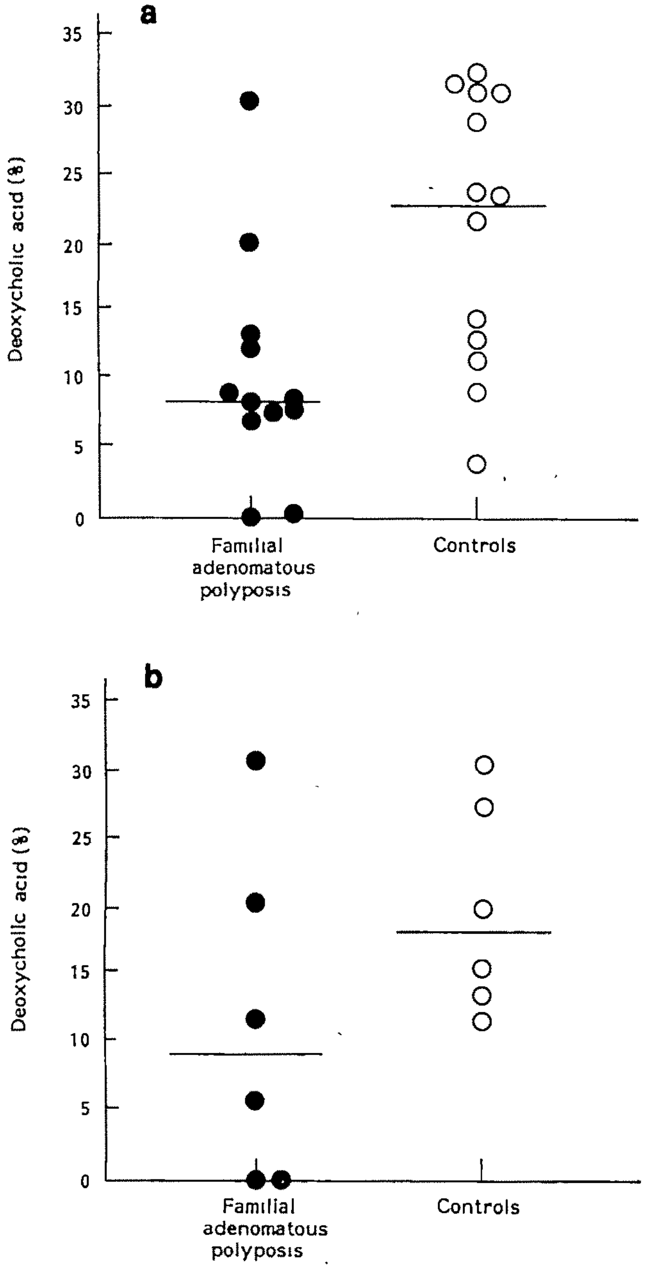

Figure 2 a *Deoxycholic acid levels in gallbladder bile were significantly different between non-age-matched patients with familial adenomatous polyposis and controls* ($P<0{\cdot}01$). *The median ages (and interquartile ranges) were, respectively, 35·5 (25–43) years and 50 (41–62) years. Statistical significance was retained after exclusion of patients with gallstones* ($P=0{\cdot}02$). **b** *Age-matching removed significance because of smaller numbers, but the trend remained the same* ($P>0{\cdot}2<0{\cdot}3$). *Horizontal bars denote median values*

Table 2 *Duodenal bile acid profiles in patients with familial adenomatous polyposis and controls*

	Age (years)	TBAA (mg/ml)	Amidates as a percentage of TBAA							
			CA	CDCA	DCA	LCA	PBA	SBA	G	T
Familial adenomatous polyposis ($n=17$)	43 (40–50)	11·9 (7–26)	49 (46–59)	45 (40–50)	1 (0–5)	0 (0–0)	99 (95–100)	1 (0–5)	78 (75–84)	22 (16–25)
Controls ($n=15$)	38 (28–58)	10·2 (6–16)	40 (35–44)	43 (34–58)	13 (8–24)	0 (0–0)	86 (76–92)	14 (8–24)	73 (63–75)	27 (25–37)
P*			<0·01		<0·01		<0·005	<0·005	<0·05	<0·05

Values are medians with interquartile ranges in parentheses. TBAA, total bile acid amidates: CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; PBA, primary bile acids; SBA, secondary bile acids, G, glycine conjugates, T, taurine conjugates. * $P>0{\cdot}05$ unless stated otherwise been reported before. Moorehead *et al.*[13] found a raised proportion of CDCA in the duodenal bile of 50 patients with colonic adenomas and 14 patients with colon cancer, the majority of whom underwent sampling after removal of tumours, compared with 50 controls. The demonstration of similar changes in our patients, in whom adenomas were present at the time of sampling, supports the assumption that these changes did not arise as a consequence of surgery.

The change in taurine conjugates on the other hand seems to be an effect of surgery. The proportion of bile acid taurine conjugates in the polyposis group decreased from a precolectomy level that was higher than that found in the control group to a postcolectomy level significantly lower than controls. This finding is consistent with rapid bile acid turnover where taurine conjugation, which is rate limited, lags behind that of glycine conjugation.

Rapid bile acid turnover, coupled with the observed significant elevation of total biliary bile acid concentration in patients with polyposis, suggests that faecal bile acid concentration should be higher in patients with polyposis than in controls. This has not been observed in three studies involving a total of 56 patients with familial adenomatous polyposis[20–22], implying that bile acids are conserved rather than excreted in these patients. Excessive internal recycling of toxic bile acids might substantially contribute to the disorders of cell growth manifest in patients with polyposis. Kinetic studies with radiolabelled bile acids are required to clarify this. Other studies of biliary bile acids have given results that conflict with those obtained by us and by Moorehead *et al.*[13]. An increase in the proportion of secondary bile acids in the duodenal bile of 11 patients with colonic adenomas and 11 age-matched controls was reported by van der Werf *et al*[12]. Moorehead *et al.* postulated that the explanation for this difference in results might be due to three patients with gallstones within the control group[13]. Although our results failed to show a statistically significant difference between patients with and patients without gallstones, perhaps because of small numbers, a trend toward higher secondary bile acids in the gallstone group was evident. Similarly, Castleden *et al.*'s analysis of the gallbladder bile of ten patients with colon cancer, 13 patients with gallstones and eight controls revealed an increase in the proportion of secondary bile acids in the gallstone group, but failed to show any significant difference between patients with colon cancer and controls[16]. However, their results have a wide scatter and patients' age data are absent (age influences bile acid metabolism)[23,24]; these features may explain the differing results obtained.

Patients with gallstones are not an ideal control group because their gallbladder function is abnormal and this affects bile acid metabolism[25]. However, exclusion of the control patients with gallbladder disease did not influence the conclusions drawn; we believe that a true difference exists in the bile acid profiles of patients with polyposis and controls

The use of duodenal bile introduces additional variables such as pancreatic and duodenal secretions. The postcolectomy status of patients with familial adenomatous polyposis undergoing screening by upper gastrointestinal endoscopy might further complicate matters, by virtue of the physiological function of the colon in bile acid metabolism To minimize the effects of these factors, bile samples from the patients with polyposis who had an intact colon (in whom pure gallbladder bile was obtained) and samples from the postcolectomy patients (from whom bile-enriched duodenal juice was taken) were analysed separately and compared with bile sampled from control groups in the same manner. Because bile acid composition differed between test and control groups in both of these circumstances, neither colectomy nor other duodenal juices account for the observed differences.

Patients undergoing elective laparotomy with an intact colon, without intestinal cancer and without gallstones, would provide a better control group for aspiration of gallbladder bile, but such patients are rare and it was not considered ethical to include them in this study. Duodenal bile from patients with polyposis who had intact colons would have also allowed a comparison of like with like, but this was not available because screening gastroduodenoscopy usually starts after colectomy (the risk of duodenal cancer being small in the first few decades of life, when colectomy is performed)[1]. When we compared patients with polyposis who had intact colons and control patients with intact colons, we were therefore able to use only the results of analysis of gallbladder bile from patients with polyposis and duodenal bile from controls. Although the same trends were found as before, statistical significance was no longer obtained. We believe that the different sources of the bile may have accounted for this. We do not think that the alternative explanation holds, i.e. that colectomy led to the differences seen when duodenal bile from patients with polyposis was compared with duodenal bile from controls, for the reasons outlined above

It has been observed that patients with colorectal cancer excrete significantly more LCA and have a higher LCA:DCA ratio in their faeces than do controls, so that the LCA DCA ratio has been advanced as a marker of high risk[11] The elevated CDCA:CA ratio found in the bile of patients with polyposis in the present study is consistent with this because LCA is a metabolite of CDCA and DCA is a metabolite of CA, these metabolites arising as a result of intestinal bacterial action on the bile acids.

The risk of intestinal neoplasia continues after colectomy The finding of similar bile acid abnormalities both before and after colectomy is consistent with a role for bile acids in the neoplastic process. Bile acids might function in this way by their presence in abnormal amounts or proportions For example, the relative proportions of bile acids have been shown to influence their comutagenic effect in the Ames salmonella mutagenicity assay with the large bowel carcinogen 1,2-dimethylhydrazine[6].

Alternatively, target cells may be hypersensitive to normal bile acid levels. Abnormal sensitivity to tumour-promoting agents has, for example, been demonstrated to be a feature of fibroblasts taken from patients with polyposis[26,27]. This has led to the hypothesis that cells from patients with polyposis are in an 'initiated state' and are therefore susceptible to the action of tumour promoters. Bile acids have been shown to be tumour promoters in some[28,29], but not all[30], animal model studies of large bowel cancer. The intestinal cells of patients with polyposis may be abnormally sensitive to agents, such as the bile acids, which cause cell proliferation[3,4].

Whether the tendency for the mucosal epithelial cells of patients with polyposis to form adenomas, which themselves are foci of abnormal cell proliferation[31], is a result of an inherited hypersensitivity to tumour promoters or arises because of abnormal concentrations of promoters, such as bile acids, or is a combination of both effects, is peripheral to the immediate problem of developing an effective treatment for duodenal polyposis

Involvement of the duodenum in polyposis poses a difficult management problem because polyps recur after surgical and endoscopic intervention. These treatment options are further limited when, as commonly occurs, polyps are located at or around the ampulla, where intervention might lead to narrowing and obstruction of pancreaticobiliary efflux. The sessile nature of many of these lesions also makes endoscopic snaring impossible. Drugs such as vitamin C[32], calcium[33] and sulindac[34], which have all been used in patients with polyposis, and in others at high risk of familial colonic cancer, to try to reduce cell proliferation and adenoma growth, may prove to be of use in this context. Dietary modification using fibre-rich diets, as used in the context of rectal polyposis[35], might also prove beneficial in treating upper gastrointestinal polyposis, perhaps via the influence of fibre on bile acid metabolism[36]. Elucidation of the basic defect responsible for the abnormal bile acid profiles should allow the development of more precise means of treatment.

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Changes in hepatic haemodynamics and hepatic perfusion index during the growth and development of hypovascular HSN sarcoma in rats

D. M. Hemingway, T. G. Cooke, S. J. Grime*, D. M. Nott† and S. A. Jenkins†

*University Departments of Surgery, Glasgow Royal Infirmary, Glasgow and †Royal Liverpool Hospital, Liverpool, and Nuclear Medicine Department, *Royal Liverpool Hospital, Liverpool, UK*

Correspondence to:
Professor T. G. Cooke, University Department of Surgery, Royal Infirmary, Glasgow G31 2ER, UK

Experimental liver tumours were induced in the Hooded Lister rat by the intraportal inoculation of 10^6 HSN sarcoma cells. The hepatic perfusion index was raised 10 days after the inoculation of cells (at the micrometastatic stage) and when overt tumour was present 20 days after inoculation. Overt tumours were hypovascular compared with normal liver. Portal venous flow and portal venous inflow fell significantly when the hepatic perfusion index was increased, but hepatic arterial flow did not alter. Portal vascular resistance and splanchnic vascular resistance were both increased in tumour-bearing animals but portal pressure, arteriosystemic shunting and portosystemic shunting did not increase significantly at any stage during the growth of hepatic tumour. These findings confirm that the hepatic perfusion index can be elevated in the presence of both micrometastatic and overt hepatic tumour and that the changes are not due to either arteriosystemic shunting or mechanical portal venous obstruction.

A substantial proportion of patients with an apparently normal liver at the time of initial surgery for removal of a primary colorectal tumour subsequently develop hepatic metastases[1,2]. In approximately 30 per cent of these patients occult metastases are present at the time of resection of the primary colorectal tumour[3]. These undetected liver metastases are the major determinant of survival. Finlay and McArdle reported that most patients with occult hepatic metastases were dead within 2 years of resection of their colorectal primary[4]. Olson *et al.*[5] found that one-third of patients developed metachronous liver metastases after apparently curative resections with only a 10 per cent 5-year survival.

Changes in the hepatic perfusion index (HPI), the relative hepatic arterial contribution to total liver blood flow, derived by dynamic hepatic scintigraphy, has been suggested as a means of identifying occult hepatic metastases[6]. Leveson *et al.* demonstrated that an abnormally elevated HPI predicted the presence of occult metastases in 96 per cent of patients in whom the metastases became apparent within 1 year after removal of the primary tumour[6]. However, the HPI was less sensitive (66 per cent) in detecting hepatic tumours appearing 2 years after initial surgery[7].

To elucidate the haemodynamic changes responsible for the changes in HPI a dynamic hepatic scintigraphy technique was developed in the rat[8]. Using Walker carcinosarcoma as the tumour model[9] it was observed that the changes in HPI resulted from a decrease in portal venous inflow, and not, as suggested by Leveson *et al.*[6] and Boyd *et al.*[10], an increase in hepatic arterial flow. In rats with hepatic tumour derived by the intraportal administration of Walker cells, the decrease in portal venous inflow was associated with an increase in portal vascular resistance secondary to increased arteriosystemic shunting[9]. In humans, hepatic metastases derived from colorectal cancer rarely exhibit significant arteriosystemic shunting[11] and are relatively hypovascular[12] compared with the hypervascular, confluent and rapidly growing Walker tumour. For this reason we investigated the haemodynamic changes associated with the development of a hypovascular liver tumour in the rat, which is more representative of human colorectal metastases.

Materials and methods

Tumour induction

Hepatic metastases were induced in male Hooded Lister rats of 200–250 g body-weight by the intraportal administration of 10^6 HSN sarcoma cells The HSN cell line was grown in a confluent monolayer in Dulbecco's modified Eagle's medium (Sigma, UK) supplemented with 10 per cent fetal calf serum, 10 mmol glutamine and penicillin/streptomycin solution in an atmosphere of 5 per cent carbon dioxide at 37°C After trypsinization the cells were administered to the rats as a single cell suspension. Viability was >95 per cent as assessed by trypan blue exclusion To ensure that liver blood flow did not change as a result of a previous laparotomy or because of the intraportal inoculation of cellular material, an additional series of rats were inoculated with dead HSN sarcoma cells, killed by rapid freezing and thawing.

Dynamic hepatic scintigraphy

The technique for performing dynamic hepatic scintigraphy in the rat has previously been reported in detail[8,9]. Briefly, after an overnight fast the rats were anaesthetized by an intraperitoneal injection of sodium pentabarbitone 30 mg/kg. A Portex cannula (Portex, Hythe, UK, outside diameter 0·61 mm) was screened into position in the left ventricle using a Siemens Sinemobile Image Intensifier (Siemens Ltd., Sunbury-on-Thames, UK) via the right carotid artery. Adequate expulsion of a bolus was assessed by injection of 0·1 ml sodium meglumide.

Dynamic hepatic scintigraphy was performed by a rapid intraventricular injection of 0·04 ml albumin colloid labelled with 80 MBq ^{99m}Tc. Images were acquired at a rate of 3 frame/s on a γ-camera with a pinhole collimator and stored on hard disk for subsequent analysis. Regions of interest (ROI) were drawn on a composite image to correspond with the left ventricle, the right kidney, the liver excluding the upper pole of the right kidney, the aorta and the lower border of the right lung Time–activity curves were drawn from these ROI and subjected to a maximum of three quadratic smooths. The gradients of the hepatic arterial and portal venous phases of the hepatic time–activity curves which are proportional to the arterial and portal venous perfusion were determined by linear regression. The HPI was calculated as the ratio of the hepatic arterial gradient to the total liver blood flow gradient. Ten animals were used in each group of normal controls and of test animals at 2, 6, 10 and 20 days after inoculation of tumour cells

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Blood flow

Immediately after completion of the dynamic hepatic scintigraphy studies a 2 Fr Portex cannula was introduced into the left femoral artery. All rats received an intraventricular injection of approximately 100000 ^{57}Co-labelled microspheres (Dupont, Germany) 15·7 μm in diameter suspended in 0·3 ml of 0·9 per cent saline with 0·01 per cent Tween over 20 s. The microspheres were ultrasonically disaggregated for 10 min before use. A reference sample of blood was withdrawn from the femoral artery at a constant rate of 1 ml/min commencing 10 s before administration of the microspheres and continued for 40 s after completion of the injection. The radioactivity in the organs and reference sample were counted in a γ-well counter (Packard, Pangbourne, UK) and organ blood flow was calculated using the method of McDevitt and Nies[13]:

$$\text{Organ flow} = \frac{\text{Organ radioactivity (c.p.m.)} \times \text{rate of withdrawal of reference blood sample (ml/min)}}{\text{Reference sample radioactivity (c.p.m.)}}$$

A difference of >10 per cent in the blood flow to the right and left kidneys indicated inadequate ventricular mixing of the microspheres and the results for those rats were rejected.

Hepatic arterial flow was determined from the counts in the liver, and portal venous inflow from the counts in the organs draining into the portal vein.

Haemodynamics

A further series of animals were inoculated with live tumour cells. Experiments were carried out on groups of 10 rats at 2, 6, 10 and 20 days after inoculation of tumour cells and on normal controls. Rats were anaesthetized with intraperitoneal sodium pentabarbitone. Through a midline laparotomy the gastroduodenal artery was mobilized and cannulated with a Portex cannula (outside diameter 0·61 mm) so that the tip lay at the bifurcation of the coeliac artery at the origin of the gastroduodenal artery. Intrahepatic arteriosystemic shunting was determined by consecutive intra-arterial injections of a non-diffusible marker, ^{99m}Tc-labelled methylene diphosphonate (MDP) and ^{99m}Tc-labelled macroaggregated albumin (MAA). Briefly, a γ-detector connected to a one-channel analyser and a microcomputer was positioned over the apex of the left lung and shielded from the liver by a lead screen. A 50 μl bolus of MDP was injected into the gastroduodenal artery, and the activity in the lungs detected by the scintillation counter was displayed on the screen. Since MDP is not retained to any great extent by the liver the computer registers the radioactivity in the lung fields as a passing fraction of 100 per cent. MAA is almost completely trapped within the liver when given regionally except when there is arteriovenous shunting. The passing fraction of MAA is thus expressed graphically as a percentage of that for MDP. We have previously established that the correlation between this technique and a conventional microsphere technique is high ($r = 0·93$). This technique allows the simultaneous measurement of arteriosystemic and portosystemic shunting within a single animal using a single isotope label.

Mean arterial blood pressure was recorded on a Gould recorder attached to a strain gauge transducer (Gould Medical Ltd., Lutterworth, UK). A cannula was placed in the portal vein via the ileocolic vein and advanced to the hilum of the liver for measurement of the portal pressure using a pressure transducer attached to a Gould recorded. Portosystemic shunting was determined by consecutive intraportal injections of ^{99m}Tc-labelled MDP and macroaggregated albumin in a similar manner to the method for arteriosystemic shunting. In previous experiments we have shown a close correlation between this technique and a conventional microsphere technique ($r = 0·90$). Portal flow was measured by placing a Gould SP2202 electromagnetic flow probe 2 mm in diameter around the mobilized portal vein cranial to the gastroduodenal vein. The flow probe was zeroed *in vivo* by occluding the portal vein distally.

Portal vascular resistance was calculated by dividing portal pressure by portal flow in individual rats.

Splanchnic vascular resistance was calculated by dividing systemic arterial pressure by portal flow in individual rats.

Histology

Representative sections of the liver were fixed in formal saline and stained with haematoxylin and eosin for histological examination.

Percentage replacement

The percentage hepatic replacement in tumour-bearing animals was calculated as

$$\frac{\text{Tumour weight}}{\text{Liver weight}} \times 100 \text{ per cent}$$

Statistical analysis

Differences between groups were analysed by an analysis of variance.

Results

Histology

No microscopic evidence of liver tumour was seen at either 2 or 6 days after inoculation of tumour cells. Micrometastatic deposits were identified in approximately 50 per cent of animals at 10 days. Discrete overt metastases were present at day 20 in all rats examined. Histological examination revealed that these were hypovascular compared with normal surrounding liver. The mean hepatic replacement by tumour was 33·6 per cent by weight at 20 days.

Hepatic perfusion index

There were significant increases in the hepatic perfusion index 10 days 47·2(12·9) (mean(s.d.)) and 20 days 53·3(9·5) after injection of the tumour cells, compared with control animals (33·3(5·2)) (*Figure 1*). The HPI 2 and 6 days after inoculation of cells was not significantly different between control animals and those injected with live tumour cells. All the individual hepatic perfusion index values for tumour-bearing rats were greater than the highest value observed in any of the control animals.

The coefficient of variation for the hepatic perfusion index in controls and experimental animals is shown in *Table 1*.

The raw counts (mean(s.e.m.)) for the kidney, liver and heart regions of interest for each of the 30 frames in each study are shown in *Table 2*.

Blood flow

The mean hepatic arterial flow in the experimental rats was not significantly different from that in control rats (2·51(0·93) ml/min) at any stage after tumour cell inoculation (*Figure 2*).

The mean blood flow to hepatic tumour (0·10(0·09) ml/min per g) was significantly less than that to the surrounding liver parenchyma (0·26(0·18) ml/min per g). The arterial blood flow

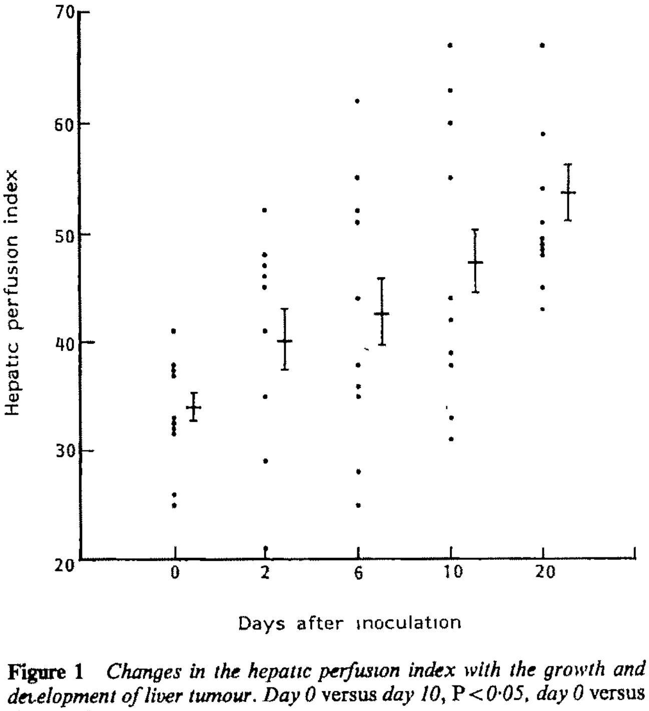

Figure 1 *Changes in the hepatic perfusion index with the growth and development of liver tumour. Day 0* versus *day 10,* P<0·05*, day 0* versus *day 20,* P<0·001

Table 1 *Coefficient of variation and ranges for hepatic perfusion index during the growth and development of hepatic tumour*

Time after inoculation (days)	Coefficient of variation (%)	Range
0	15·5	25–41
2	23·6	21–52
6	28·0	25–62
10	27·3	31–67
20	17·6	43–67

Table 2 *Raw counts (mean(s.e.m.)) for kidney, liver and heart regions of interest*

Kidney	Liver	Heart
544·8(29·7)	366·0(24·6)	1403(138·0)

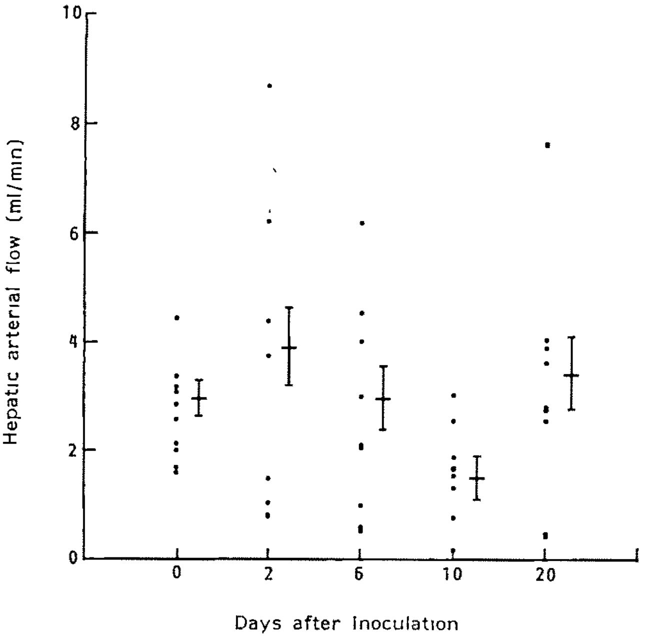

Figure 2 *Changes in hepatic arterial flow during the growth and development of liver tumour*

to liver tissue in experimental rats at all stages during the growth and development of liver tumour was not significantly different from that to the normal liver parenchyma in control animals (0·26(0·09) ml/min per g) (*Figure 3*).

Portal venous inflow in rats with overt tumour (2·38(1·60) ml/min) was significantly lower than that observed in control rats (7·65(3·90) ml/min, $P<0·001$) or experimental animals 2 days after inoculation of the tumour cells (6·72(3·79) ml/min, $P<0·01$) (*Figure 4*).

The hepatic perfusion index, hepatic arterial flow and portal venous inflow in normal control animals and in animals inoculated with dead cells are shown in *Table 3*.

There were no significant differences in HPI, hepatic arterial flow or portal venous inflow between normal control animals and at any stage after inoculation of dead tumour cells.

Haemodynamics

Portal venous flow (*Table 4*) was significantly lower in the rats with micrometastases at 10 days (8·2(2·20) ml/min, $P<0·05$) and those with overt tumour at 20 days (7·65(2·30) ml/min, $P<0·01$) compared with control rats (14·8(3·60) ml/min). There was a slight but non-significant rise in mean portal pressure

Table 3 *Hepatic perfusion index, hepatic arterial flow and portal venous inflow in control animals and animals after intraportal inoculation of dead HSN sarcoma cells*

Time after inoculation (days)	Hepatic perfusion index	Hepatic arterial flow (ml/min per g)	Portal venous inflow (ml/min per g)
0 (control)	33·3(1·6)	0·22(0·03)	0·56(0·2)
2	33·7(4·5)	0·29(0·04)	0·62(0·12)
6	29·9(5·4)	0·23(0·036)	0·64(0·12)
10	26·3(4·0)	0·13(0·04)	0·45(0·04)
20	30·0(5·0)	0·31(0·07)	0·56(0·09)

Values given are mean(s.e.m.)

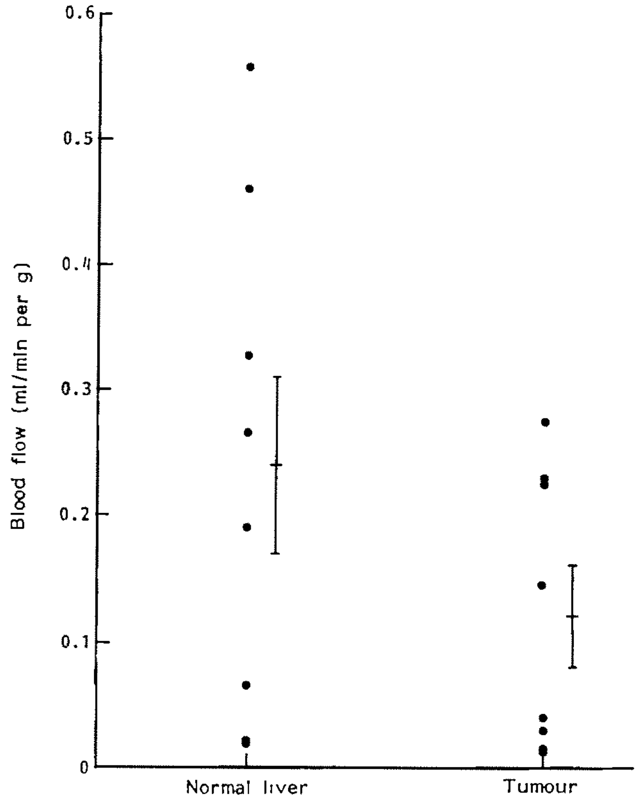

Figure 3 *Arterial flow to tumour and normal liver* * P<0·01 *(compared with normal liver)*

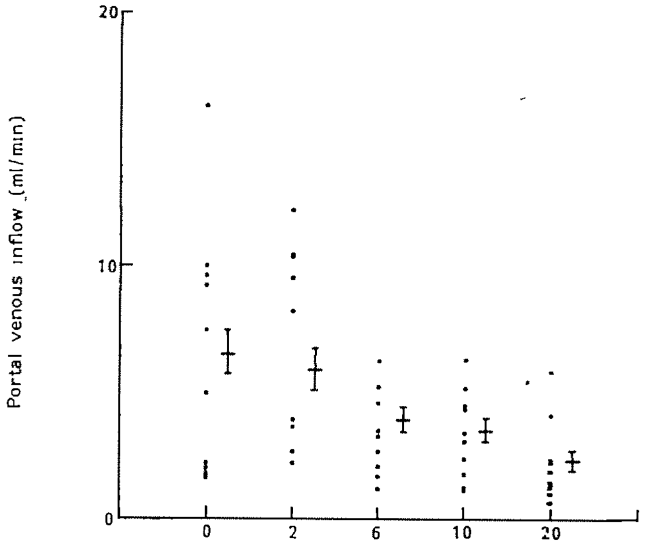

Figure 4 *Changes in portal venous inflow during the growth and development of liver tumour. Day 0 versus day 20,* P<0·05; *day 2 versus day 20,* P<0·01

Table 4 *Portal pressure, portal venous flow, portal vascular resistance and splanchnic vascular resistance in control rats and rats developing hepatic tumour*

Time after inoculation (days)	Portal pressure (mmHg)	Portal flow (ml/min)	Portal vascular resistance (mmHg/ml per min)	Splanchnic vascular resistance (mmHg/ml per min)
0 (control)	7·9(0 85)	14·8(0 9)	0·55(0 07)	6 96(0·88)
2	7 82(1·2)	14·9(0 7)	0 51(0 09)	5·78(1 8)
6	8 35(0·63)	11·6(0 6)	0·75(0 08)	6·7(1 3)
10	9 4(0·95)	8·2(0·6)*	1·38(0 16)*	9 1(2 9)
20	10·4(1 6)	7·65(0·7)†‡	1 62(0·43)†	12·8(2 2)*

Values given are mean(s.e.m.). *$P<0\cdot05$, †$P<0\cdot01$ (*versus* day 0), ‡$P<0\cdot05$ (*versus* day 2)

Table 5 *Arteriosystemic shunting and portosystemic shunting in control rats and rats with developing hepatic tumour*

Time after inoculation (days)	Arteriosystemic shunting (% units)	Portosystemic shunting (% units)
0 (control)	8·1(1·1)	6 7(1·3)
2	5·8(3·3)	3·2(1·2)
6	5 2(1·04)	7·1(2·2)
10	7·8(2·5)	6 0(1·4)
20	7 0(2·2)	3·6(1 1)

Values given are mean(s.e.m.)

(*Table 4*) in rats with overt tumour (10·4(5·10) mmHg) compared with that in control animals (7·9(2·70) mmHg) Portal vascular resistance (*Table 4*) in rats 10 days after inoculation (1·38(0·51) mmHg/ml per min, $p<0\cdot05$) and in rats with overt tumour (1·62(1·35) mmHg/ml per min, $P<0\cdot01$) was significantly higher than in control animals (0·55(0·23) mmHg/ml per min). Splanchnic vascular resistance (*Table 4*) in rats with overt tumour (12·8(7·60) mmHg/ml per min) was significantly greater than in control animals (6·96(2·80) mmHg/ml per min, $P<0\cdot05$).

Arteriosystemic shunting

The passage of MAA through the liver (arteriosystemic shunting, *Table 5*) was 8·1(3·50) per cent units in control animals. The degree of shunting was not significantly different in rats with micrometastases (7·8(2·50) per cent) or those with overt tumour (7·0(4·50) per cent).

Portosystemic shunting

Portosystemic shunting in control animals was 6·7 per cent and remained unchanged during the growth and development of the tumour (*Table 5*).

Discussion

Previous studies in both experimental animals and in humans have confirmed that the hepatic perfusion index is elevated in the presence of hepatic tumour. Leveson *et al.*[6] demonstrated that the hepatic perfusion index was abnormally elevated in patients with apparently disease-free livers who developed hepatic metastases within 1 year after resection of their primary colorectal tumour. Some patients who developed hepatic metastases in the second year after their initial operation had a normal HPI at diagnosis of the primary colorectal tumour Our previous studies in rats with hepatic tumour derived from intraportal administration of Walker cells confirmed that the HPI is elevated in the presence of micrometastases and remains abnormally high during the subsequent growth of these micrometastatic deposits into overt tumour[9]. These studies used Walker cells which grow rapidly, are hypervascular and produce confluent liver tumour[9]. In the present study HSN sarcoma cells were used which produce a slower growing discrete hypovascular tumour probably more representative of human metastases from colorectal primaries. In addition to confirming an elevation in the HPI in large overt tumours, the results also support the previous findings in humans that the hepatic perfusion index may not be abnormal in the early phase of the development of slow-growing hepatic tumours. The findings suggest that slow-growing tumours influence hepatic haemodynamics at a much later stage than rapidly growing hypervascular tumours. Since hypovascular tumours are often found in humans[14,15,16], the results of this investigation suggest that there is a need for repeated measurements of the hepatic perfusion index in patients with an initially 'disease-free' liver and a normal result. It would appear that the development of liver tumour in humans and experimental animals results in abnormalities in liver blood flow Although attempts have been made to estimate the hepatic arterial and portal venous components of liver blood flow from the relative flow data generated by dynamic hepatic scintigraphy[17], accurate quantification of the underlying haemodynamic changes is difficult in humans because of the invasive nature of the techniques used. To elucidate the haemodynamic changes responsible for the alterations in the HPI in the presence of hepatic tumour necessitates the use of appropriate animal models.

Breedis and Young[13] were the first to report that hepatic tumour has a predominantly arterial supply. On this basis both Leveson *et al.*[6] and Sarper *et al.*[18] postulated that during the growth of tumour within the liver the change in the hepatic perfusion index would result from an increase in hepatic arterial flow to tumour-bearing liver. Estimates of hepatic arterial flow in patients with liver metastases have also suggested that hepatic arterial flow may increase in the presence of liver metastases[18]. This hypothesis can now be discounted since the results of this study and that of Nott *et al.*[9] have shown that the change in the hepatic perfusion index is due primarily to a decrease in portal venous flow. These data also suggest that the arterial perfusion to normal liver surrounding liver metastases is similar to that of liver parenchyma in control animals and is therefore unaffected by the development of liver tumour.

The present study clearly demonstrates that the hepatic perfusion index can change in the absence of arteriosystemic shunting although portal vascular resistance is increased. Arteriosystemic shunting cannot therefore be the cause of the reduction in portal flow and portal venous inflow associated with liver metastases in hypovascular tumours.

An alternative explanation for the reduction in portal venous inflow in the presence of tumour is intrahepatic mechanical obstruction of the portal system. There is experimental evidence that both portal venous compression and invasion by growing liver tumour may mechanically obstruct blood flow and decrease portal venous inflow[16]. The data presented in this study do not support this hypothesis.

In experimental animals portal venous obstruction caused by partial portal vein ligation results initially in a decrease in portal venous inflow and a rise in portal pressure[19]. The portal pressure gradually declines after partial ligation of the portal vein because of the formation of an extensive collateral circulation. Portal hypertension remains, however, because of an increased splanchnic blood flow secondary to an increase in cardiac output. This clearly did not occur in this study because the portal pressure in tumour-bearing animals was not significantly higher than in control animals. There was no formation of a collateral circulation because portosystemic shunting was not increased. Any intrahepatic resistance to portal flow resulting from the growth of the tumour is therefore insufficient to increase portal pressure significantly.

Although portal pressure was not significantly elevated, the decrease in portal venous inflow in tumour-bearing animals was associated with a significant rise in splanchnic vascular resistance which, as discussed above, is unlikely to be due to mechanical obstruction. It is possible that the increase in splanchnic vascular resistance in the presence of tumour may be related to other factors, such as the release of vasoactive agents which elicit splanchnic vasoconstriction. Further studies are required to clarify the precise mechanism of the changes in hepatic blood flow in the presence of liver metastases.

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Tumour necrosis factor increases hepatic cell mass

K. Mealy* and
D. W. Wilmore

Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, Massachusetts 02115, USA
Correspondence to:
Dr D. W. Wilmore

The effect of tumour necrosis factor (TNF) on hepatic cellularity was investigated in male Wistar rats maintained on total parenteral nutrition. Twenty-eight rats were infused with TNF (2×10^5 units TNF-α kg^{-1} $24\ h^{-1}$) or saline (controls) for 6 days. Wet and dry liver weights and nitrogen content were significantly increased by TNF ($P < 0{\cdot}001$), indicating an increase in liver mass. A further 81 rats were infused with TNF (2 or 4×10^5 units kg^{-1} $24\ h^{-1}$) or saline over 1, 3 and 6 days. Total liver DNA and protein content and counts of hepatocyte mitosis were determined. Liver DNA and protein increased with dose of TNF and time ($P < 0{\cdot}001$), suggesting that TNF increased hepatic cellularity. Histological examination demonstrated no significant inflammatory infiltrate to account for the increased cell mass. However, the number of hepatocyte mitoses increased with dose of TNF and time ($P < 0{\cdot}05$), indicating that the increase in liver cellularity was due to increased hepatocyte cell number. TNF-induced hepatic hyperplasia appears to be an additional feature of the integrated host response to injury and infection.

Following infection, major trauma and burn injury a series of characteristic metabolic host responses occurs[1]. One important feature of these responses is the shift of protein from skeletal muscle to liver, presumably to fuel gluconeogenesis and new protein synthesis[2]. Initially it was thought that the 'stress' hormones (glucagon, catecholamines and glucocorticoids) were responsible for many of these changes[3]. However, recently it has become apparent that cytokines are important mediators of these events. Cytokines are polypeptide products of activated lymphocytes, macrophages and other cell types which stimulate cell growth and initiate immunological, endocrinological and metabolic responses. The cytokines, interleukins 1, 2 and 6 and tumour necrosis factor (TNF), have been particularly implicated in metabolic responses to illness[4–7].

TNF is particularly interesting because it is a major mediator of many of the host responses to Gram-negative sepsis and endotoxic shock[7–9]. TNF is known to induce hepatic acute phase protein synthesis[10,11] but in addition we have noticed that chronic infusion of this cytokine in rats gives rise to marked hepatomegaly. The object of these studies was to determine the specific effects of TNF on hepatic cellularity.

Materials and methods

Two studies were carried out in 200 g male Wistar rats ($n = 109$) which had external jugular venous catheters inserted under phenobarbital anaesthesia[12]. The animals were then allowed to recover for 24 h. To ensure constant identical nutritional intake the rats were then commenced on total parenteral nutrition (TPN) containing adequate calories and nitrogen for growing rats (404 kJ non-protein energy and 0·985 g nitrogen per 100 ml, infused at a rate of 48 ml $24\ h^{-1}$)[12]. Before each study the rats were randomized to either control or TNF groups (recombinant human TNF-α, Asachi Chemical Industries Incorporated, New York, USA). The control animals received the TPN solution with saline and the TNF-infused animals received the TNF mixed in the TPN solution; previous studies indicated no loss of bioactivity when the TNF was administered in this manner. All animals had free access to water throughout the study.

Study 1

TNF (2×10^5 units kg^{-1} $24\ h^{-1}$, $n = 10$) or 0·9 per cent saline ($n = 18$) was infused over 6 days and the animals were then killed and the livers were removed and weighed. The fresh livers were placed in a drying oven for 24 h at 90°C and reweighed when dry. Total liver nitrogen content was measured on the dry samples by the macro-Kjeldahl method[13].

Study 2

Eighty-one additional rats were randomized into control (TNF 0 group) and TNF groups. TNF was administered at doses of 2 or 4×10^5 units kg^{-1} $24\ h^{-1}$ (TNF 2, TNF 4 groups). Selected animals were killed after 1, 3 and 6 days of infusion. The livers were weighed and portions of liver homogenate were used for the determination of DNA and protein using the methods of Burton[14] and Lowry *et al.*[15]. Total DNA and protein content were calculated assuming the DNA and protein:tissue weight ratios were constant throughout the entire liver parenchyma. Additional portions of liver tissue were fixed and stained with haematoxylin and eosin. Counts of hepatocyte mitoses were carried out in a blinded fashion; results are expressed as the mean of ten high power fields counted.

Statistical methods

Results are expressed as mean(s.e.m.). One way analysis of variance (ANOVA) was used for comparison of means at a single time-point and two way ANOVA was used to examine group effects with time[16]. The Dunnett *t* test was used for *post-hoc* comparisons when necessary.

Results

Eighty-eight of the 109 animals entered into the study survived until they were killed. In the control group 97 per cent survived whereas this decreased to 74 and 75 per cent respectively in the TNF 2 and TNF 4 groups.

Liver weights and nitrogen content

TNF increased wet and dry liver weights and total liver nitrogen content reflecting the hepatomegaly observed in these animals (*Table 1*). The increase in both wet and dry liver weights indicated that this effect was not due to fluid retention alone. Total liver nitrogen content was also significantly increased in the TNF 2 group in comparison with controls, indicating increased protein content (*Table 1*).

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Table 1 *Wet and dry liver weights and total liver nitrogen content in control (TNF 0 group) and TNF-infused (TNF 2 group) animals at 6 days*

Group	Wet liver weight (g)	Dry liver weight (g)	Liver nitrogen (mg)
TNF 0 ($n=10$)	9·19(0·3)	2·53(0·2)	268·4(19·2)
TNF 2 ($n=18$)	13·72(0·7)*	3·61(0·2)*	440·3(30·2)*

Values are mean(s.e.m.); TNF, tumour necrosis factor; * $P<0·001$ *versus* TNF 0

Table 2 *Total liver DNA and protein in the TNF groups and control group (TNF 0) after 1, 3 and 6 days of infusion*

	Controls		Infused animals			
	TNF 0	*n*	TNF 2	*n*	TNF 4	*n*
DNA (g in total liver)*						
Day 1	27·0(1·5)	10	27·6(1·3)	10	25·5(1·3)	11
Day 3	25·9(1·4)	9	36·8(1·8)	9	43·3(2·7)	12
Day 6	18·9(0·5)	6	64·6(4·1)	6	49·6(4·0)	8
Protein (g in total liver)*						
Day 1	1·50(0·52)		1·60(0·83)		1·50(0·50)	
Day 3	1·54(0·04)		1·76(0·13)		2·05(0·12)	
Day 6	1·22(0·07)		2·15(0·19)		1·77(0·15)	

Values are mean(s.e.m.); TNF, tumour necrosis, factor; * $P<0·0004$ (TNF group effect *versus* controls)

Liver DNA and protein

TNF infusion increased both total liver DNA and protein content (*Table 2*). No response was observed after 24 h of infusion; however, after 3 days, hepatic DNA and protein content increased in a dose-dependent fashion with TNF. After 6 days of TNF infusion, maximal DNA and protein responses were observed in the TNF 2 group. The changes in both liver DNA and protein content suggest increased liver cellularity.

Histological examination

Hepatocyte mitosis counts increased with duration of TNF infusion whereas few mitoses were seen in the control animals (*Table 3*). Binuclear cells indicating recent nuclear division also increased with duration of TNF infusion. Increased hepatocyte mitosis was apparent in the TNF 2 group after 3 and 6 days of infusion; the greatest response occurred in this group after 3 days. Hepatocyte mitosis increased in the TNF 4 group after 24 h of infusion and was also maximal at 3 days. No appreciable influx of inflammatory cells was seen in either of the TNF-infused groups throughout the study indicating that this cell type was not responsible for the increased hepatic DNA and protein content. A characteristic histological section from a TNF-infused animal at 3 days is shown in *Figure 1*.

Discussion

This study demonstrates that TNF increases liver cell mass. Because liver nitrogen increased by 160 per cent following TNF infusion over 6 days it is unlikely that changes of this magnitude could be due to increased secretory proteins alone. The increased DNA and protein content and counts of hepatocyte mitosis would indicate that this response is due to an increase in hepatocyte cell number. This effect was dose dependent after 3 days of TNF infusion whereas after 6 days of infusion the greatest response occurred in the lower dose TNF-infused group.

It is likely that these changes occur in association with increased hepatic acute phase protein synthesis as described by others[10,11]. The importance of the liver and this response is underlined by the compensatory hypertrophy demonstrated in this study. The exact purpose of hepatic acute phase protein production is unknown, although its presence in all species following diverse inflammatory stimuli, and its preservation even in the severely malnourished subject, indicate that it has important survival benefits[17]. Although TNF has not been shown to induce the full array of acute phase proteins *in vitro*[10,11], it has been shown to induce interleukin 6 both *in vitro*[20,21] and *in vivo*[6]. Interleukin 6, previously known as hepatocyte stimulating factor or β_2-interferon, is the most potent acute phase protein stimulant[18,19]. Therefore TNF-induced hepatic hyperplasia may be a direct action of this cytokine or due to TNF-induced secondary mediators such as interleukin 6. While glucocorticoids may have a permissive role in this response, other studies indicate that TNF-induced liver hyperplasia cannot be replicated by glucocorticoids or the other stress hormones alone[22,23].

Little attention has previously been focused on the structural changes that occur in the liver in association with hepatic acute phase responses. Liver weight increases in the first few days after infection[24], and it is interesting to note that the doses of TNF infused in this study initiated clinical features of sepsis in the TNF-infused animals which accounted for the increased mortality rate in this group[25]. Furthermore, these TNF doses are comparable to those released *in vivo* in other species following endotoxin administration[26]. Another potent inflammatory stimulus is burn injury, and this has also been shown to increase hepatocyte mitotic rate[27]. Others have demonstrated

Table 3 *Counts of hepatic mitosis in the control (TNF 0) and TNF-infused groups (TNF 2, TNF 4) at 1, 3 and 6 days of infusion*

	Controls		Infused animals			
	TNF 0	*n*	TNF 2	*n*	TNF 4	*n*
Hepatocyte mitoses*						
Day 1	0·13(0·07)	6	0·07(0·07)	6	0·63(0·19)	7
Day 3	0·08(0·08)	5	1·28(0·27)	5	0·89(0·47)	7
Day 6	0·10(0·08)	4	0·53(0·18)	3	0·20(0·20)	5

Values are mean(s.e.m.); TNF, tumour necrosis factor; * $P<0·05$ (TNF group effect *versus* controls)

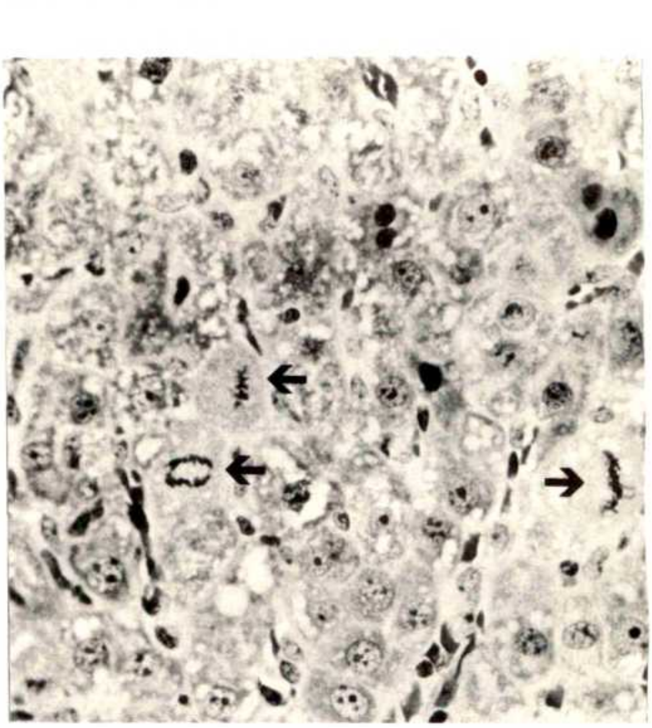

Figure 1 *Haematoxylin and eosin histological section from a rat liver infused with tumour necrosis factor (TNF) (group TNF 2) after 3 days of infusion. Hepatocyte mitosis (arrows) is increased in the TNF-infused animals*

that TNF increases hepatic DNA content, but the authors attributed this to an accumulation of inflammatory cells[28,29]. Histological examination of liver sections in the present study did not demonstrate increased inflammatory infiltration throughout the liver parenchyma or within the periportal regions. Differences in TNF dose and route of administration may account for the variations observed.

In addition to effects on the liver, TNF also has important effects on fat[30], carbohydrate[31] and protein[22] metabolism. These responses may be direct or via alterations in stress hormone release. It has been postulated that the substrate changes induced by skeletal muscle catabolism, namely increased glucose production and increased availability of free fatty acids, occur to fuel hepatic protein production, immune proliferation and wound healing, and that they are essential components of the metabolic response to critical illness[32]. Increased understanding of cytokine biology may help explain the integration of these events.

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Oestrogen receptor D5 antibody is an independent negative prognostic factor in gastric cancer

J. D. Harrison,
J. A. Jones, I. O. Ellis
and D. L. Morris*

Department of Surgery, University Hospital, Nottingham, UK and
**School of Surgery, St. George Hospital, Kogarah, New South Wales, Australia*

Correspondence to.
Mr J. D. Harrison, Department of Surgery, University Hospital, Nottingham NG7 2UH, UK

Recent studies have demonstrated oestrogen receptors in tissues other than those considered to be sex hormone responsive, for instance in gastric cancer. In vitro *experiments have shown oestradiol to be trophic to gastric cancer cell lines. The effect of D5 (an oestrogen receptor-related protein) status on survival was therefore studied in a group of 188 consecutive patients undergoing surgery for gastric cancer. Ninety-two patients (49 per cent) were positive for the D5 antibody. There were no differences between the D5-positive and D5-negative groups for age or adverse prognostic features such as high grade tumours or advanced stage. The D5-negative patients had a significant survival advantage over the D5-positive patients. The 95 per cent confidence interval for survival in the patients with D5-negative tumours was 63–101 weeks compared with 39–66 weeks for the patients with D5-positive tumours (Mantel–Cox statistic = 4·15,* P = *0·042). Prognostic factor analysis with a Cox proportional hazards model showed tumour stage* (P = *0·001) and D5 status* (P = *0·003) to be significant independent factors in gastric cancer. Laurén type, grade and gender were not significant independent factors in this small series.*

The presence of oestrogen receptors in sex hormone responsive organs such as breast and prostate is well recognized. Endocrine manipulation plays an integral part in the management of neoplastic disease in these organs

In the past 10 years studies have concentrated on examination of tissues other than those regarded as sex hormone responsive for evidence of oestrogen receptors. Significant concentrations of high affinity oestrogen receptors have been found in a variety of malignant tissues including oesophageal squamous cell carcinoma[1], adenocarcinoma of stomach[2–5], pancreas[6], colon[7–11], kidney, malignant melanoma, and a variety of soft tissue sarcomas[12].

A recent study[5], using a specific monoclonal antibody to oestrogen receptors[13] (ER-ICA, Abbott Laboratories, Berkshire, UK) showed receptors in 28 per cent of gastric adenocarcinomas, particularly in poorly differentiated lesions. The patients with oestrogen receptor-positive tumours had a significantly worse prognosis than those with oestrogen receptor-negative tumours.

A recently described monoclonal antibody (D5)[14], raised against partially purified myometrium, reacts with a cytosolic fraction related to the nuclear oestrogen receptor, and its presence has been shown to indicate the likelihood of response to endocrine therapy in oestrogen receptor-positive breast cancer[15].

We have studied 188 consecutive patients undergoing surgery for gastric cancer with regard to D5 status and survival to examine the hypothesis that oestrogen receptor status (by the D5 antibody) may be a prognostic marker.

Patients and methods

One hundred and eighty-eight consecutive patients with a diagnosis of gastric adenocarcinoma were included in the study and underwent resection where possible (67 per cent resection, 8 per cent bypass, 12 per cent intubation, 13 per cent inoperable).

All patients were followed regularly in the outpatient clinic, with death being the principal endpoint in the study.

Immunohistological method

The D5 antibody was used because it is effective on fixed material embedded in paraffin blocks and has been demonstrated to be a reliable and reproducible technique[16] The resected tumours were fixed in 10 per cent formal calcium for 24 h.

Tissue blocks were processed routinely into paraffin wax and sections were cut at 4 μm Sections from all the blocks sampled were stained with haematoxylin and eosin for assessment of histological grade and tumour type based on the Laurén classification[17]

Representative blocks bearing tumour were selected from each case for immunohistological examination. These sections were stained with the D5 antibody using a two-stage indirect immunoperoxidase method with imidazole enhancement[18]. The primary antibody, D5 (Amersham International, Amersham, UK), was applied in ascitic fluid diluted one in 1000. The second-stage peroxidase-conjugated rabbit antibody (Dako UK Ltd., London, UK) was diluted to 1 in 1000. Both were diluted with 1 in 20 normal swine serum in tris hydrochloric acid saline buffer, pH 7·6 The sections were counterstained with haematoxylin

Omission of the primary antibody was used as a negative control for each case and a section of human breast carcinoma of known immunoreactivity was used as a positive control.

All sections were assessed in a semiquantititative manner by one pathologist, based on the number of cells staining in the section. A positive result occurred where more than 25 per cent of the cells stained with the D5 antibody The categories used were negative, focal staining and diffuse staining.

Statistical analysis

The survival data were analysed using the Kaplan–Meier product limit method[19]. The Mantel–Cox generalized Savage test was used to test for significance of survival differences between groups

A Cox proportional hazards model was used to analyse the survival data or independent prognostic factors. The covariates used in the model were stage, D5 status, gender, Laurén type and histological grade.

Results

One hundred and eight-eight consecutive patients were entered into the study, of whom 135 were male and 53 were female. Of these patients, 78 per cent have now died with a mean follow-up

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Table 1 *Demographic data of D5-positive and D5-negative patients*

	D5-positive	D5-negative
Gender		
Males	62	73
Females	30	23
Laurén type		
Intestinal	54	39
Diffuse	29	44
Mixed	9	13
Differentiation		
Poor	64	68
Moderate	20	16
Not stated	8	12
Stage		
Early gastric cancer	2	1
Wall only	10	14
Lymph node metastases	25	30
Liver metastases	23	18
Inoperable	32	33

of 67 weeks, and a median length of survival of 26 weeks. The D5-positive and D5-negative groups were well matched for gender, stage, differentiation and Laurén type (*Table 1*)

Of the 188 tumours evaluated for oestrogen receptor (D5) status, 92 (49 per cent) were positive. Sixty-two (46 per cent) of the males and 30 (57 per cent) of the females had D5-positive tumours ($\chi^2 = 1{\cdot}73$, n s.).

There was no significant difference in the mean age of patients in the two groups. The 95 per cent confidence interval for the ages of patients in the D5-positive group was 69–73 years, and 67–72 years for the D5-negative group

There was no difference in the proportion of D5-positive tumours in the poorly differentiated group compared with D5-negative tumours (64 (70 per cent) of D5-positive tumours and 68 (71 per cent) of D5-negative tumours were poorly differentiated).

Tumour stage did not affect the proportion of D5-positive tumours (wall only 42 per cent positive, lymph node metastases 45 per cent, liver metastases 56 per cent, inoperable 49 per cent).

The patients who were D5 negative had a significant survival advantage over the D5-positive patients. The 95 per cent confidence interval for survival in those with D5-negative tumours was 63–101 weeks compared with 39–66 weeks for positive tumours (Mantel–Cox statistic = 4·15, $P = 0{\cdot}042$). *Figure 1* shows the survival of patients according to lymph node status (Mantel–Cox statistic = 4·2, $P = 0{\cdot}0405$) and *Figure 2* shows the survival of the patients according to D5 staining characteristics.

The prognostic factors derived from a Cox proportional hazards model are shown in *Table 2*; stage and D5 status are significant and independent prognostic factors. Laurén type, histological grade and gender failed to reach significance as prognostic factors independent of stage and D5 status.

Discussion

Many early studies of oestrogen receptors in gastrointestinal tumours used the dextran charcoal suspension method High affinity receptors in significant concentrations that were lower than the levels found in breast cancer were demonstrated[3,7]

Doubts existed about immunohistological methods because it was felt the detected 'receptor' was not necessarily the true high affinity binding to 'type I' receptor, but rather lower affinity (two or three times) binding to types II and III receptors, which do not represent specific binding[20].

Recent studies using monoclonal antibodies have detected cytosolic proteins which are related to the oestrogen receptor. The monoclonal antibody D5 was raised against a soluble oestrogen receptor component. It is an immunoglobulin G class of antibody which reacts with a non-glycosylated serine phosphoprotein of 29 kD in the cytosol. This 29 kD protein was found to be related to, but not part of, the oestrogen receptor

This antibody has a significant correlation with oestrogen receptors assayed by ligand binding[21] and in breast cancer, D5 antibody positivity has the same correlation with prognosis as oestrogen receptor positivity defined by traditional biochemical methods[15]

The significance of the finding of oestrogen receptors and receptor-related proteins in gastric adenocarcinoma remains uncertain, but it would be associated with the production of proteins which bind oestradiol in the neoplastic cells

Human gastric adenocarcinoma cell lines are stimulated to grow by increasing concentrations of oestradiol[22] and the presence of the receptor could therefore be a factor resulting in an increased rate of tumour growth, perhaps accounting for the poorer prognosis in patients with receptor (or receptor-related protein) positive tumours

The significance of progesterone receptors in gastric cancer is unknown but may be an indicator that the oestrogen receptor in the same cell is functioning. If the situation is analogous to breast cancer, tumours with both oestrogen and progesterone receptors are more hormone responsive[22].

Studies with human gastrointestinal cancer cell lines have shown that oestradiol does have a trophic effect on these cells and that this effect is amplified rather than inhibited by tamoxifen[23].

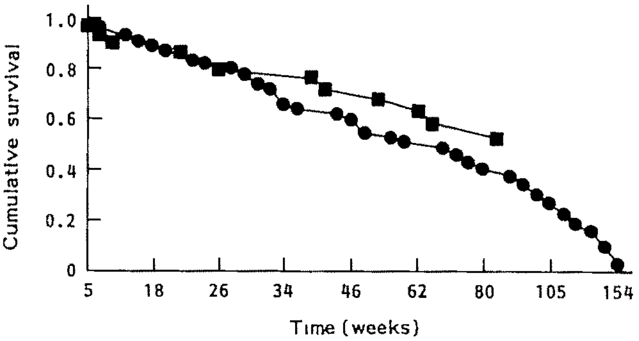

Figure 1 *Cumulative survival plot of patients with lymph node negative* (■) *and lymph node positive* (●) *tumours*

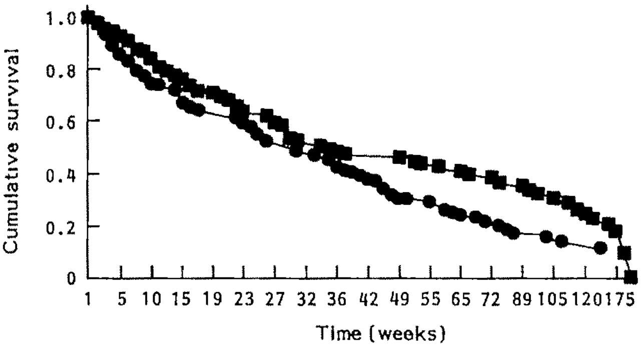

Figure 2 *Cumulative survival plot of patients with D5-negative* (■) *and D5-positive* (●) *tumours*

Table 2 *Prognostic factors derived from a Cox proportional hazards model*

	Coefficient/SEM	*P*
Stage	8·12	0·001
D5 status	−2·95	0·003
Differentiation	−1·38	0·17
Laurén type	1·01	0·31
Gender	0·69	0·50

A recent Japanese study examined the use of adjuvant tamoxifen with chemotherapy in patients with diffuse gastric carcinoma and showed a survival advantage (43 *versus* 6 per cent at 3 years) for the treated patients[2]. This was a small study, however, and was not adequately controlled. Our randomized study of tamoxifen therapy showed no survival advantage for the treated patients[24]. The control patients in this study had no other treatment and it is possible that in the Japanese study the tamoxifen was acting as a mitogen (as in our cell cultures), potentiating the effect of the cytotoxic chemotherapy.

The D5 status is a significant independent prognostic factor in patients with gastric cancer. Whether this has any relationship to the ability of tumours to respond to hormonal manipulation is an important future clinical question.

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Suturing or stapling in gastrointestinal surgery: a prospective randomized study

West of Scotland and Highland Anastomosis Study Group

University Department of Surgery, Western Infirmary, Glasgow, Gartnavel General Hospital, Glasgow, Raigmore Hospital, Inverness, Crosshouse Hospital, Kilmarnock, Inverclyde Royal Hospital, Greenock and Royal Alexandra Hospital, Paisley, UK

Correspondence to:
Professor W D George, University Department of Surgery, Western Infirmary, Glasgow G11 6NT, UK

A prospective randomized study of 1004 patients is reported, comparing surgical stapling and manual suturing techniques in the construction of gastrointestinal anastomoses. The incidence of clinical leaks was similar between the two groups (sutured 3·2 per cent, stapled 4·7 per cent; $P=0{\cdot}22$*), while for radiological leaks the incidence was significantly higher in the sutured group (12·2 per cent* versus *4·1 per cent,* $P<0{\cdot}05$*). Stapling instruments afforded significantly quicker anastomoses, mean(s.e.m.) 28·1(0·7)* versus *14·3(0·5) min* ($P<0{\cdot}001$)*, and quicker operations, 115·5(2·4)* versus *103·8(2·2) min* ($P<0{\cdot}001$)*. The two groups were found to be comparable in other respects such as operative mortality, requirements for blood transfusion, incidence of infective complications, recovery of gastrointestinal function and postoperative hospital stay.*

The introduction of modern stapling instruments in the early 1970s has led to a rapid increase in the application of stapling techniques to clinical practice. Although stapling has become a recognized alternative to conventional manual suturing in the construction of gastrointestinal anastomoses, its appropriate place in clinical practice remains to be defined.

A number of benefits conferred by the use of stapling instruments, such as minimizing tissue manipulation and trauma, less bleeding and oedema at the anastomosis, a quicker return of gastrointestinal function and a more rapid patient recovery, have all been claimed by the manufacturers. Conversely, stapling techniques have been criticized on the grounds of expense[1], that no improvement in anastomotic security has been observed and that there is the possibility of stricture formation[2–4]. Good clinical evidence upon which to base these claims and counterclaims remains hard to find. Several retrospective reviews have reported variable results[5–7]. Of the few prospective randomized trials[8–13] comparing surgical stapling and manual suturing techniques, the majority have focused on large bowel surgery[8–11] and the use of circular stapling instruments. Furthermore, convincing conclusions cannot be drawn from any of these prospective studies due to their small samples sizes.

The aim of this study, therefore, was to compare surgical stapling with manual suturing in a prospective randomized fashion in a large population of patients undergoing both elective and emergency gastrointestinal surgery.

Patients and methods

Patients

Any patient under the care of a participating surgeon who was undergoing elective or emergency surgery which was likely to result in a gastrointestinal anastomosis was considered eligible for study. A total of 1161 patients was studied between April 1985 and April 1989.

Participating surgeons

At the start of the study there were seven participating surgeons from three surgical units (one academic surgical unit and two district general hospital units). During the course of the trial a further six surgeons from two additional centres joined the study. The participating surgeons were not particularly selected because of a specific gastrointestinal interest, but were general surgeons, some with non-gastrointestinal interests such as breast disease, transplantation, vascular surgery or urology.

Preoperative assessment

Preoperative assessment consisted of recording simple anthropometric parameters including height, weight and the presence and amount of weight loss. In addition, routine haematological and biochemical data including serum albumin were collected. These parameters were measured to enable subsequent analysis of the comparability of the randomized groups.

Preoperative preparation

All patients undergoing upper gastrointestinal procedures received a single dose of 1·5 g cefuroxime intravenously with the induction of anaesthesia. For large bowel surgery antibiotic prophylaxis consisted of 1 g cefotaxime and 500 mg metronidazole intravenously at the time of induction of anaesthesia and repeated twice at 8-h intervals thereafter.

Elective large bowel surgery patients were restricted to a low-residue liquid diet together with tea and water 48 h before surgery. In the absence of an obstructing lesion they were also given 500 ml 10 per cent mannitol solution orally on the afternoon of the day before surgery. Patients with obstructing lesions had bowel wash-outs only.

Randomization

A stratified randomization technique was used. Each participating surgeon was assigned an equal number of sealed envelopes indicating sutures or staples. For each surgeon these envelopes came in four separate surgical categories, namely oesophageal, upper gastrointestinal (including biliary anastomoses), colonic and colorectal. Randomization took place at the time of surgery only when the surgeon was satisfied that either anastomotic technique was feasible and equally appropriate. In those patients in whom one or other technique was considered to offer a particular advantage randomization did not take place and the preferred anastomotic technique was used. These non-randomized patients were studied in an identical way to the randomized group but were analysed separately.

Anastomotic techniques

All stapled anastomoses were constructed using combinations of the GIA®, TA® and EEA® series of stapling devices (Auto Suture Company, Ascot, UK). For sutured colocolic and colorectal anastomoses a single layer interrupted technique using 2/0 or 3/0 braided polyamide (Nurolon®, Ethicon Ltd., Edinburgh, UK) was used. In upper gastrointestinal surgery and in ileocolic anastomoses a one- or two-layered technique was used (depending on the surgeon's individual preference) with continuous 2/0 polyglycolic acid (Dexon Plus®, Davis and Geck, Gosport, UK) and/or 2/0 polyamide.

For each anastomosis recordings were made of its site in the gastrointestinal tract, its mode of construction and the time taken to complete it. Anastomotic time was defined as the time taken from the end of dissection until a complete anastomosis had been achieved. Total

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operating time, defined as the time from the start of the skin incision to the completion of the skin closure, was recorded The grades of surgical and anaesthetic staff were recorded as were any surgical and anaesthetic complications which occurred during the procedure. For colorectal anastomoses the level from the anal margin as estimated by the surgeon was documented along with any use of a defunctioning stoma

Anastomotic integrity

A clinical leak was defined as anastomotic dehiscence confirmed by either reoperation or autopsy, development of an enterocutaneous fistula, appearance of bowel contents from drains, or systemic sepsis in association with peritonitis

In patients undergoing oesophageal or colorectal anastomoses, anastomotic integrity was also assessed by contrast radiography in the period between 4 and 14 days after operation. Any extravasation of contrast medium from the anastomosis in the absence of any of the criteria for a clinical leak was recorded as a radiological leak.

Morbidity

Infective complications, including their local and systemic manifestations, were recorded as part of a sepsis score system[13]. Wound infection was defined as a purulent discharge from the incision, irrespective of bacteriological assessment, which occurred before discharge from hospital. Blood transfusion requirements and the day of discharge or death were documented. For patients with malignant disease the stage, grade and fixity of the tumours were recorded.

Return of gastrointestinal function

After operation the return of gastrointestinal function was assessed in upper gastrointestinal surgery by recording the first day that oral intake exceeded 1 l For lower gastrointestinal surgery the corresponding assessment was performed by recording the day on which the patient first passed flatus or stool.

Statistical methods

All data were collected prospectively in a uniform fashion and recorded on a standard patient record form. Data entry was performed centrally in Glasgow and any inconsistencies were resolved in discussion with the individual investigators. At the close of recruitment a 10 per cent random sample of the study patients was selected and key study variables (operative procedure, clinical leaks, etc.) were checked against the original case notes as a form of audit of the data recording

Leak rates and 30-day mortality rates were analysed using logistical regression to investigate the effects of technique (suturing *versus* stapling) and category (oesophageal, upper gastrointestinal, colonic and colorectal) Anastomosis and operating time were analysed using two-way analysis of variance to investigate the effects of technique and category as above. Confidence intervals were obtained for the leak and mortality rates in the stapled groups relative to the corresponding rates in the sutured groups using the technique described by Morris and Gardner[15]

To give adequate statistical power to detect a difference between true leak rates of 5 per cent and 10 per cent at a 5 per cent significance level, a sample size of 1000 randomized patients was chosen at the outset of the study.

Results

A total of 1161 patients were eligible for study. In 157 randomization was considered inappropriate and one or other anastomotic technique or a combination of techniques was chosen electively. Of the remaining 1004 patients, 496 had sutured anastomoses and 508 had stapled anastomoses. Six patients in the stapled group had sutured anastomoses for a variety of reasons (three instrument/technical failures, two unsatisfactory anastomoses requiring reconstruction and one randomization error). None of these patients developed anastomotic complications. In accordance with the 'intention to treat' principle these patients were considered with the stapled group for the purpose of the analysis. The distribution of sutured and stapled cases in each of the four categories is outlined in *Table 1*. There were 52 oesophageal, 300 upper gastrointestinal, 428 colonic and 224 colorectal anastomoses.

Patient characteristics for the sutured and stapled groups are outlined in *Table 2*. The groups were well matched in terms of baseline characteristics.

Table 1 *Distribution of randomized patients*

Surgical category	No. of patients Sutures	 Staples	 Total
Oesophageal	25	27	52
Upper gastrointestinal	150	150	300
Colonic	208	220	428
Colorectal	113	111	224
Total	496	508	1004

Table 2 *Patient characteristics*

	Sutured ($n=496$)	Stapled ($n=508$)
Mean(s.d.) age (years)	63·7(15·8)	65·3(14·5)
Male/female	231/265	238/270
Mean(s d.) weight (kg)	60·9(13·8)	62·7(13·8)
Mean(s d.) haemoglobin (g/dl)	12·9(2·0)	12·9(2·1)
Mean(s d.) WBC count ($\times 10^9$/l)	8·9(3·6)	8·9(3·6)
Mean(s.d.) albumin (g/l)	37·8(5·5)	37·5(5·7)
Patients with malignant disease (%)	67	66
Patients having emergency surgery (%)	22	19

WBC, white blood cell

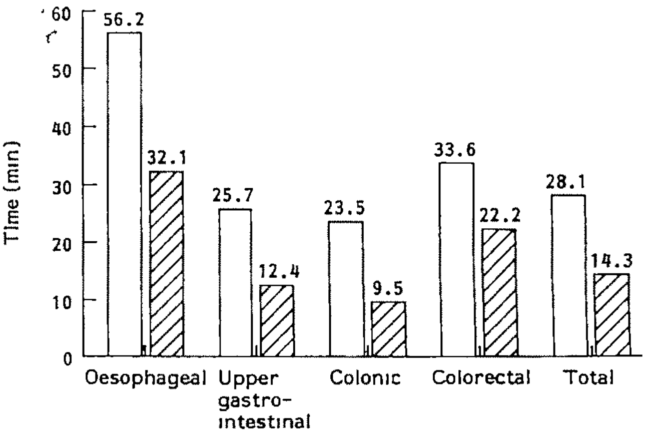

Figure 1 *Mean time for sutured* (□) *and stapled* (■) *anastomoses in each of the four surgical categories*

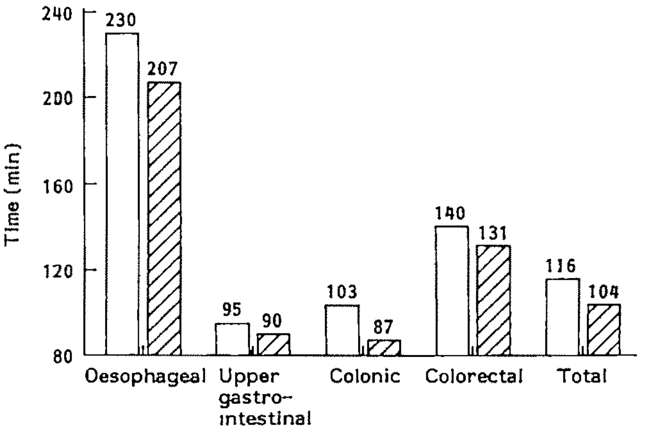

Figure 2 *Mean operating time for suturing* (□) *and stapling* (■) *in each of the four surgical categories*

Anastomosis and operating times

Figures 1 and *2* give the corresponding mean times for the entire sutured and stapled groups and also the times for the four subgroups. The overall mean reduction in anastomosis time in the stapled group was 13·8 min (95 per cent confidence interval

12·2–15·5 min) and the mean reduction in operating time was 11·6 min (95 per cent confidence interval 5·2–18·0 min). Both these differences are statistically significant ($P<0·001$). Two-way analysis of variance of the anastomosis times showed that the time saving varied between the four categories ($P<0·01$), the largest saving being in the oesophageal group and with broadly similar savings in the other groups. A similar pattern was observed in operating time but because of the larger variability this was not statistically significant.

Consultants were present to perform or directly supervise the anastomosis during the operations in 401 (80·8 per cent) of the sutured cases and 420 (82·7 per cent) of the stapled cases.

Anastomotic integrity

Among the 1004 randomized cases, 40 (4 per cent) patients developed clinically evident anastomotic leaks The clinical leak rates were 3·2 per cent (16 of 496) in the sutured group and 4·7 per cent (24 of 508) in the stapled group ($P=0·22$). In the 52 patients undergoing oesophageal anastomoses there was only one leak which occurred in the stapled group. In colocolic anastomoses there were slightly fewer clinical leaks associated with the use of staples (six of 220) when compared with sutures (nine of 208) A reverse trend was seen in colorectal anastomoses with a lower clinical leak rate in the sutured group (five of 113) when compared with the stapled group (nine of 111). These differences were not significant and when all anastomoses involving the large bowel were considered together, the clinical leak rates were virtually identical.

A more noticeable difference in clinical leak rates was apparent in patients having upper gastrointestinal surgery. Of 150 patients having sutured anastomoses there were two clinical leaks compared with eight in 150 patients who had a stapled anastomosis. Seven of the eight leaks in the stapled group occurred in 53 patients who had closure of the duodenal stump. This compares with only one duodenal stump leak in 35 patients with sutured duodenal closure.

Figure 3 shows the ratio of stapled to sutured leaks and corresponding confidence intervals in each of the four surgical categories. There was no evidence of a differential effect of anatomotic technique between these four subgroups ($P=0·12$).

The incidence of clinical leakage in emergency and elective surgery is illustrated in *Table 3*. No significant differences were noted between the emergency and elective situation The presence or absence of a consultant at the time of operation had no significant effect on the incidence of clinical leak in either group.

Table 3 *Incidence of clinical leaks* (%)

	Sutures	Staples
Elective surgery ($n=878$)	3·1	4·6
Emergency surgery ($n=126$)	3·6	5·2
Consultant present ($n=821$)	3·2	4·5
Consultant absent ($n=183$)	3·2	5·7

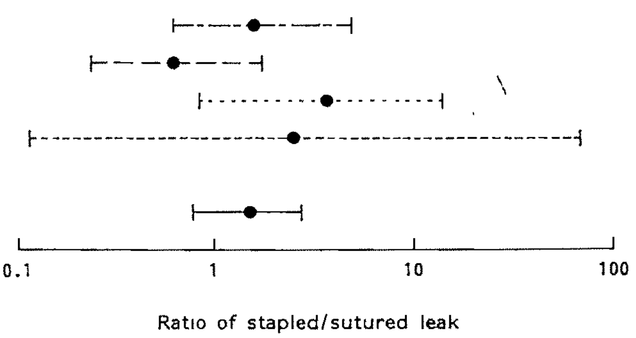

Figure 3 *Clinical leaks. ratio of stapled to sutured leaks and 95 per cent confidence intervals in each of the four surgical categories;* ——, *all patients;* ——, *oesophageal,* · · ·, *upper gastrointestinal;* ——, *colonic;* – – – – – – –, *colorectal*

Radiological leaks

Of the 224 patients with colorectal anastomoses, 186 had contrast radiography, as did all of the patients with oesophageal anastomoses. Of those with oesophageal anastomoses only one patient (sutured) had a radiological leak. Of the 186 patients with colorectal anastomoses, 18 had a radiological leak (13 in the sutured group and five in the stapled group) This difference (12·2 per cent *versus* 4·1 per cent) was statistically significant ($P<0·05$). It should be noted that individual patients with a clinical leak (as well as a radiological leak) were not included in this analysis. It should also be noted that none of the patients with a radiological leak (but not a clinical leak) suffered any related morbidity.

Mortality

The overall 30-day mortality in the randomized patients was 5·5 per cent. There was no significant difference between the sutured and stapled groups, 4·6 per cent *versus* 6·3 per cent respectively, ($P=0·23$). The observed 30-day mortality rate in the stapled group was 1·36 times that observed in the sutured group with a 95 per cent confidence interval of 0·81–2·29 for this ratio. There was no evidence of a differential effect of stapling between the four categories ($P=0·44$).

The higher mortality rate recorded in the upper gastrointestinal surgery group as a whole reflects a substantial proportion of cases in this group with either advanced gastric or pancreatic cancer. In the total upper gastrointestinal group there were 27 deaths and 10 clinical leaks. Only five of the 27 deaths were attributed directly to anastomotic breakdown Of the 652 patients with large bowel anastomoses there were 28 deaths and 29 clinical leaks. Eight of the 28 deaths were attributable to anastomotic breakdown. In total, therefore, 13 of the 55 deaths were attributable to anastomotic dehiscence while the remaining 42 were due to other causes, principally cardiorespiratory failure.

Morbidity

A modified sepsis score was used in an attempt to make a cumulative and objective assessment of postoperative complications. The mean(s.e.m.) modified sepsis score was 4·0(0·2) in the sutured group and 4·3(0·2) in the stapled group. The respective incidences of wound infection for patients in the sutured and stapled groups were 10·5 per cent and 11·8 per cent ($P=0·17$).

The distribution of patients requiring blood transfusion was similar in both groups. There were, however, five patients who required reoperation after stapled upper gastrointestinal anastomoses because of bleeding from the staple line

Return of gastrointestinal function

In patients with oesophageal or upper gastrointestinal anastomoses, similar proportions in the sutured and stapled groups were able to tolerate an oral intake of greater than 1·1 per 24 h by the fifth day after operation (56·7 per cent) of patients with sutured and 56·9 per cent of patients with stapled anastomoses). Similar proportions of patients in the sutured and stapled large bowel surgery groups had recovered gastrointestinal function by the fifth day (83·7 per cent and 86·1 per cent respectively).

Other variables

The distribution of numerous other variables between the groups was also examined (*Table 4*), not only to check comparability but also to assess whether the use of one or other technique correlated in any way with outcome. The duration of hospital stay and the use of abdominal drains were similar in both groups. The proportions of defunctioned colorectal anastomoses in the two groups were not significantly different although in the sutured group of colorectal anastomoses a

Table 4 *Perioperative variables*

	Sutures	Staples
Mean(s.e.m.) hospital stay (days)	13·6(0·4)	14·1(0·5)
Use of abdominal drains (%)	48	45
Defunctioning stoma (%)	17·7	13·5
Tumour stage (large bowel) (%)		
Dukes' A	9·0	10·1
Dukes' B	42·7	47·0
Dukes' C	32·2	29·5
Metastatic disease	16·1	13·4
Level of anastomoses (colorectal) (%)		
0–5 cm	10	19
5–10 cm	41	43
> 10 cm	49	38

Table 5 *Non-randomized patients' distribution*

	Sutured	Stapled	Combined	Total
Oesophageal	8	7	5	20
Upper gastrointestinal	15	25	17	57
Colonic	18	10	2	30
Colorectal	20	27	3	50
Total	61	69	27	157

proximal stoma was created in 17·7 per cent of patients compared with 13·5 per cent in the stapled group. The use of neostigmine or spinal anaesthesia, the mean height of colorectal anastomosis from the anal margin, and the tumour stage for those patients with malignant disease, were similar in both groups.

Audit of data recording

The audit of the recording of data carried out on a 10 per cent random sample following the termination of patient recruitment revealed few errors. On four occasions the anastomotic sites had been entered incorrectly or incompletely and the gender for one patient had been marked incorrectly.

Non-randomized patients

Of the 1161 patients who were eligible for entry into the study, 157 were not randomized. These patients had electively sutured or stapled anastomoses or a combination of both techniques. The distribution of the non-randomized cases in the four subgroups is illustrated in *Table 5*. Of the 157 patients, 61 were sutured, 69 were stapled and 27 patients had a combination of both suturing and stapling during the construction of a single anastomosis or had multiple anastomoses created by a combination of the two techniques.

There was a total of 15 clinical leaks among the 157 non-randomized patients. This clinical leak rate (9·6 per cent) is higher than that for the 1004 randomized patients (4·0 per cent). Seven of the 15 non-randomized anastomoses which leaked were sutured, six were stapled and two were combined procedures. The mortality for non-randomized patients was 8·3 per cent and that for the randomized group was 5·5 per cent. The higher clinical leak rate and higher mortality rate in the non-randomized patients cannot be explained by a higher proportion of emergency operations. It may be partially explained by a higher proportion of patients in the non-randomized group who had surgery which involved multiple anastomoses.

Discussion

While attempts have been made to evaluate stapling methods[5–7], few studies have attempted to compare surgical stapling and manual suturing techniques in a prospective randomized fashion. Reiling and colleagues in 1980[17] initiated a study in which triangulated end-to-end stapled anastomoses were compared with manually sutured anastomoses. This trial was prematurely terminated at 100 patients without showing any differences between the two anastomotic techniques. The EEA circular stapling device was assessed and compared with suturing techniques in the construction of colorectal anastomoses in the two prospective randomized studies carried out by Beart and Kelly[8] from the Mayo Clinic and Everett *et al.*[10] from Cambridge. No difference in the incidence of anastomotic leaks between the two techniques was found in these studies. The former study demonstrated that the staples enabled significantly quicker anastomoses; the operating time was shown to be significantly shorter in the latter study. Brennan and colleagues[9] from Scarborough were the first to compare suturing and stapling techniques for all large bowel anastomoses. In that study the SPTU Russian circular stapling instrument was compared with single layer interrupted suturing technique. Again the groups were found to be similar in terms of anastomotic leaks. However, suturing afforded significant advantages with respect to wound infection rate and duration of hospital stay. In another study of colorectal anastomoses with the EEA stapling instrument McGinn *et al.*[11] from Southampton found a higher incidence of both clinical and radiological leak rates with the stapling instrument. There appear to be some conflicting results in these previous prospective controlled trials and because of relatively small patient numbers no consensus has been reached.

The present study was carried out in one academic surgical unit and four district general hospitals, none of which was a specialist institution for gastrointestinal surgery. The participating consultants all had some preliminary experience with surgical stapling before the study but only one could be regarded as a regular stapler user. All junior staff working with the participating consultants contributed to the project. The operations were usually but not exclusively performed or supervised by consultants and all gastrointestinal operations, emergency or elective, were included in the trial. The situation during the current study was thought to reflect average surgical practice in the UK.

Clearly, in addition to anastomotic technique[18], the integrity of an anastomosis is influenced by a range of other variables[19–21]. For this reason variables such as antibiotic prophylaxis, bowel preparation and anastomotic technique were standardized. The stratified randomization technique whereby each participant contributed equal numbers of sutured and stapled cases in each of the four surgical categories was used to eliminate any bias which might have been introduced as a result of surgeon-related variability.

The overall incidence of clinically evident anastomotic leakage (4 per cent) in this study compares favourably with most reported series[1,6,16,22,23]. A number of factors may be responsible for this. First, there was an element of selectivity in the randomized study in which only anastomoses suitable for both suturing and stapling techniques were investigated. Secondly, the well defined 'audit effect'[24] may have played a role, favourably influencing the results.

There was no significant difference in the incidence of clinical anastomotic leaks between the sutured and stapled groups although the radiological leak rate was significantly higher in those patients with sutured anastomoses. There were, however, some features of the distribution of clinical leakage which are worthy of further comment. In patients with colorectal anastomoses the clinical leak rate was lower in the sutured group. Although the use of a defunctioning stoma was not significantly different between the sutured and the stapled groups, stomas were more commonly used in the sutured group (17·7 per cent *versus* 13·5 per cent) and this may have a bearing on the lower clinical leak rate observed in these patients.

Among the upper gastrointestinal anastomoses a more detailed analysis of the distribution of clinical leakage is revealing. Among 51 biliary enteric anastomoses and 75 gastroenterostomies there were no leaks. Two clinical leaks occurred with small bowel anastomoses, one in each of the sutured and stapled groups. The remainder of the upper gastrointestinal clinical leaks occurred from duodenal stumps and seven of these were in the stapled group. The records of these seven patients were subsequently examined and in three potential causes for duodenal stump leakage were identified. In one, postoperative intra-abdominal sepsis from another source may have played a role. In another postoperative bleeding and impaired perfusion may have been a factor and in the third the use of electrocautery in the vicinity of the staple line may have influenced the development of a subsequent leak.

Another important consideration in the choice of anastomotic technique is the cost. Although the construction of anastomoses with stapling instruments is more expensive than using suture material, when analysed in the context of the total cost of patient care stapling instruments constitute approximately 5 per cent of the total expense of the entire hospital admission. Another important element of cost analysis relates to the length of hospital stay. No differences were noted between the two groups in terms of the mean day of discharge. Day of discharge is, however, a relatively poor indicator of anastomotic healing or patient recovery because for a substantial number of patients hospital stay may be prolonged due to social or domestic factors.

In summary, this prospective randomized study has demonstrated that the use of stapling instruments produces results which are comparable with conventional hand suturing in terms of anastomotic dehiscence. Uncomplicated radiological leakage in patients with colorectal anastomoses was significantly higher in the sutured group but whether this is of importance in the long term remains to be determined. The use of stapling instruments resulted in significantly faster anastomoses and operations, although the size of these differences is not large and is perhaps unlikely to translate into more efficient use of theatre time. In practice the final selection of anastomotic technique is likely to be multifactorial, taking into account considerations such as speed, ease of construction, personal preference, cost and the training of junior surgical staff in both methods.

The following contributed to the study: A. M. Akyol, Registrar in Surgery, Western Infirmary, Glasgow, G. Bell, Consultant Surgeon, Inverclyde Royal Hospital, Greenock, J. A. Bradley, Consultant Surgeon, Western Infirmary, Glasgow; D. J. Galloway, Consultant Surgeon, Gartnavel General Hospital, Glasgow; W. D. George, Professor of Surgery, Western Infirmary, Glasgow; J. R. C Logie, Consultant Surgeon, Raigmore Hospital, Inverness; S. G. Macpherson, Senior Lecturer in Surgery, Western Infirmary, Glasgow; J R. McGregor, Lecturer in Surgery, Western Infirmary, Glasgow; K. G. Mitchell, Consultant Surgeon, Royal Alexandra Hospital, Paisley; C. G. Morran, Consultant Surgeon, Crosshouse Hospital, Kilmarnock; J. J. Morrice, Consultant Surgeon, Inverclyde Royal Hospital, Greenock, A. Munro, Consultant Surgeon, Raigmore Hospital, Inverness; G. D. Murray, Senior Lecturer in Medical Statistics, University of Glasgow; W R. Murray, Senior Lecturer in Surgery, Western Infirmary, Glasgow; J Ritchie, Research Fellow, Western Infirmary, Glasgow; B. A. Sugden, Consultant Surgeon, Crosshouse Hospital, Kilmarnock; P. V. Walsh, Consultant Surgeon, Raigmore Hospital, Inverness

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Comparison of a single layer continuous hand-sewn method and circular stapling in 580 oesophageal anastomoses

A total of 611 patients with carcinoma of the oesophagus or gastric cardia were operated on between July 1982 and December 1989. Resection was performed in 491 patients (one-stage, 483; two-stage, eight), bypass operation in 97, and 23 had exploration alone. The anastomoses of 580 patients with one-stage resection and bypass operations were evaluated. Hand-sewn anastomosis using a single layer of continuous absorbable monofilament suture was performed in 304 patients (221 resections and 83 bypasses). A stapled anastomosis was performed on 276 patients (262 resections and 14 bypasses). Following resection, there were 11 (5 per cent) anastomotic leaks in the hand-sewn group and ten (3·8 per cent) in the stapled anastomosis group (P = *0·69). Excluding anastomotic leaks, hospital mortality and anastomotic recurrence, stricture occurred in 18 of 172 hand-sewn anastomoses (10·5 per cent) and in 57 of 195 stapled anastomoses (29·2 per cent)* (P < *0·001). In patients who had bypass operations there were 12 anastomotic leaks, ten in the hand-sewn group (12·0 per cent) and two in the stapled anastomosis group (14·3 per cent). Only two of the discharged patients with bypass developed anastomotic strictures, a low incidence probably because of short survival. In addition, there were 245 subsidiary anastomoses made in the abdomen by the hand-sewn method as part of the reconstructive procedure, and there was one leak. The results of this non-randomized study suggest that hand-sewn anastomosis using a single layer continuous technique for the oesophagus is as safe as the use of circular staplers; hand-sewn anastomosis is less likely to become stenotic.*

M. Fok, A. K. Ah-Chong, S. W. K. Cheng and J. Wong

Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

Correspondence to:
Professor John Wong

Following resection or bypass operations for cancer of the oesophagus, the anastomosis is performed by a hand-sewn technique or by the use of circular staplers. Traditionally, a hand-sewn anastomosis is fashioned using one, two or even three layers of interrupted sutures[1]; these multilayered anastomoses can be technically cumbersome and have a higher leakage rate than stapled anastomoses[2]. Following stapled anastomosis, mucosa-to-mucosa apposition is not achieved and necrotic tissue is present between the cut edge and the staples. In addition the non-absorbable steel staples are placed circumferentially thus inhibiting dilatation. If a stapled anastomosis can achieve low leakage rates, we surmised that the simplest method of restoring continuity, using a single continuous layer of hand-sewn suture which ensures direct mucosal contact, should suffice[3] Circular stapling, in addition, is associated with an increased incidence of stricture formation which is size-dependent[4].

Patients and methods

Between July 1982 and December 1989, 611 patients with carcinoma of the oesophagus or gastric cardia were operated on There were 491 patients who underwent resection and reconstruction; 483 had a one-stage procedure and eight had two-stage operations. Of the remaining patients 97 had bypass operations for unresectable tumours and 23 had exploration alone. In the analysis of hand-sewn *versus* stapled anastomosis only patients who had undergone one-stage resection and reconstruction or bypass operations were evaluated.

The choice between hand-sewn or stapled anastomosis was determined by the site of anastomosis, the size of the oesophageal lumen, and local tissue factors For example, hand suture was preferred for cervical anastomosis as the use of the stapler in the neck is restricted by the confined space and the limitation imposed by the length of the substitute 'oesophagus'. Hand suture was also used for the small sized oesophagus or when the oesophageal wall was oedematous or hypertrophic. On the other hand, a circular stapler was used when surgical exposure and tissue conditions were optimal, for anastomosis high in the apex of the pleural cavity, and when the oesophageal lumen was sufficiently wide. The largest size circular stapler that could be accommodated in the oesophagus was chosen[5]. On this basis of selection, the types of anastomoses employed for different procedures and their locations would not be evenly distributed as shown in *Table 1*

The hand-sewn anastomosis was made using a single layer of continuous absorbable monofilament sutures of either 4/0 Maxon® (polyglyconate, Davis and Geck, Cyanamid, Gosport, UK) or 4/0 PDS® (polydioxanone, Ethicon Ltd , Edinburgh, UK) Two single-armed sutures were tied together at their ends to form a double-armed suture. The divided proximal end of the oesophagus and the oesophageal substitute (stomach, colon or jejunum) were anastomosed starting at one lateral angle and the posterior layer was completed first The suture picked up the full thickness of the oesophagus and the substitute, taking 5 mm bites from the luminal edge at 5 mm intervals with mucosal inversion This was continued until a third of the way across the anterior layer, after turning around the opposite lateral corner. The remaining anterior layer was completed with the second suture taking the full thickness of the oesophagus but only the seromuscular layer of the substitute Apposition was maintained with minimal tension on the suture[3]. In all, 304 patients had a hand-sewn oesophageal anastomosis; 221 were patients undergoing resection (45·0 per cent of the resection group), and 83 were patients undergoing bypass (85 6 per cent of the bypass group).

The other 276 patients had a stapled anastomosis; 262 patients

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having resection and 14 patients having bypass. Altogether 131 EEA® (Autosuture, US Surgical Corporation) and 145 ILS® (Ethicon Ltd., Edinburgh, UK) circular staplers were used by a technique which has been previously described[5]

When the stomach was unsuitable or unavailable as an oesophageal substitute, colon or small bowel was used. For colonic and the majority of small bowel interpositions, three anastomoses were necessary These were an upper (oesophageal) anastomosis, a lower (gastrocolic, gastrojejunal or duodenojejunal) anastomosis, and a third anastomosis to re-establish continuity of the intestinal tract from which the substitute had been taken. When a bypass operation was performed using stomach, there was usually an oesophagojejunal and a jejunojejunal anastomosis in the abdomen, in addition to a cervical anastomosis. These anastomoses, which were in addition to the primary anastomosis of oesophagus to substitute, were also examined in this study. The subsidiary anastomoses were all performed with the same hand-sewn method.

A gastrografin swallow or flexible endoscopy was performed on 481 (83 per cent) patients at about 10 days after operation. A diagnosis of anastomotic leakage was made on clinical evidence and supported by gastrografin swallow or endoscopy where appropriate. After discharge, patients were followed up every second week for 2 months, then every month for 1 year, and subsequently at intervals of 3 months. Those who had any symptoms related to swallowing were endoscoped and, when indicated, also had a barium study. A diagnosis of benign anastomotic stricture was made in symptomatic patients who, on endoscopy, were found to have narrowing of the anastomosis through which a 10 mm diameter flexible endoscope could not be passed. These strictures were dilated under local anaesthesia and sedation. In the evaluation of postoperative stricture formation, patients who died in hospital and those with anastomotic leaks or anastomotic recurrence were excluded

Statistical differences between the two groups were determined by the χ^2 test or Fisher's exact test when the numbers were small.

Results

The types of resection and the technique of anastomosis used in the different operations are shown in *Table 1*. Hand-sewn oesophageal anastomosis was performed in the majority of patients who required an anastomosis in the neck. In about three-quarters of the operations involving an anastomosis in the chest, circular staplers were used.

Table 2 summarizes the level of oesophageal anastomosis, the incidence of leakage and the number of fatal leaks in the hand-sewn and stapled groups. There were 11 anastomotic leaks in the hand-sewn group (5·0 per cent), and in six patients this complication proved fatal. There were ten leaks with stapled anastomoses (3·8 per cent) and three patients died of this complication. Grouped together, three of six leaks in neck anastomoses, three of 11 leaks in chest anastomoses, and three of four leaks following abdominal anastomosis were fatal. The difference in the incidence of leaks between hand-sewn and stapled anastomoses was not statistically significant ($P = 0·69$). The incidence of leaks and the number of leaks with fatal outcome between different levels of anastomosis were also not significantly different.

Table 1 *Type of resection and anastomotic technique*

	No. of patients	
	Hand-sewn	Stapler
Lewis–Tanner operation	50	194
Transhiatal oesophagectomy	61	7
Oesophagogastrectomy	39	24
Abdominal gastrectomy	30	30
3-phase oesophagectomy	28	0
Split sternum oesophagectomy	11	4
Other resection	2	3
Total	221	262

Table 2 *Anastomotic leakage after oesophageal resection*

	Hand-sewn		Stapler	
Site of anastomosis	No. of patients	No. with leakage	No. of patients	No with leakage
Neck	111	6 (3)	11	0
Chest	80	4 (2)	221	7 (1)
Abdomen	30	1 (1)	30	3 (2)
Total	221	11 (6)	262	10 (3)

Numbers in parentheses indicate fatal leaks

Table 3 *Anastomotic stricture after oesophageal resection**

	Hand-sewn		Stapler	
Site of anastomosis	No. of patients	No. with stricture	No of patients	No with stricture
Neck	81	11	11	3
Chest	67	6	161	54
Abdomen	24	1	23	0
Total	172	18	195	57

* Hospital mortality, anastomotic leak and anastomotic recurrence excluded

In addition to fatal anastomotic leaks, there were 25 hospital deaths in the hand-sewn group and 40 hospital deaths in the stapled group. These deaths were mostly due to cardiopulmonary complications or malignant cachexia. The overall 30-day and hospital mortality rates were 5·0 per cent and 14·0 per cent respectively for hand-sewn anastomosis, and 5·0 per cent and 16·4 per cent respectively for patients with stapled anastomosis. Anastomotic recurrence occurred in 15 patients (6·8 per cent) with hand-sewn and 17 patients (6·5 per cent) with stapled anastomosis; the difference was not statistically significant.

After anastomotic leaks, hospital mortality and anastomotic recurrence were excluded, the incidence of anastomotic stricture formation was assessed (*Table 3*). Of the 172 patients in the hand-sewn group, there were 18 anastomotic strictures (10·5 per cent), while of the 195 patients in the stapled group, 57 (29·2 per cent) developed strictures. All strictures were symptomatic and required dilatation. The majority of these narrowings produced symptoms in the early postoperative period (median 3·5 months). The difference in the incidence of anastomotic stricture between hand-sewn and stapled groups was significant ($P < 0·001$).

In patients who had only bypass operations, the anastomoses were all fashioned in the neck There were 12 anastomotic leaks, ten from a hand-sewn (12 per cent incidence) and two from a stapled anastomosis (14·3 per cent incidence). Seven of the patients died because of the leakage. The 30-day and hospital mortality rates for patients undergoing bypass surgery were high at 29 per cent and 50 per cent respectively. The majority of these patients fell victim to cardiopulmonary complications or advancing malignancy. Only two of the 49 discharged patients developed an anastomotic stricture However the median survival in this group of patients was only 2·4 months.

There were 245 subsidiary anastomoses as part of the reconstructive procedure (*Table 4*). These were performed in 97 patients who had bypass operations and 41 who had resections as described above. One leak (0·4 per cent) occurred in a colocolic anastomosis and proved fatal.

Discussion

Leakage rates of between 14 per cent and 23 per cent have been reported following the use of hand-sewn oesophageal anastomosis[6–9] with a correspondingly high attendant morbidity and mortality[10–12], but some reports are less pessimistic[13,14]. Not all authors have favoured a continuous suturing technique[15,16].

Table 4 *Leakage of subsidiary anastomosis*

	No. of patients	No. with leakage
Oesophagojejunal	36	0
Gastrojejunal	5	0
Duodenojejunal	12	0
Jejunojejunal	54	0
Gastrocolic	67	0
Ileocolic	39	0
Colocolic	32	1
Total	245	1 (0·4%)

The advent of the circular stapler has been associated with a consistent lowering of anastomotic leakage rates to between zero and 3·5 per cent[2,4,17]. With experience, stapling devices are relatively easy to use and may shorten operating time. The stapled anastomosis is standardized and of reproducible quality. It avoids large bites of tissue being embraced by sutures and may achieve less inversion. Unfortunately, a decreased risk of anastomotic leak is associated with the complication of stricture formation, the reported incidence of which has ranged from 10 per cent to 14 per cent[4,17–19]. The likelihood of stricture formation has been shown to be inversely proportional to the size of the stapler used which, in turn, is dictated by the size of the oesophagus[4]

The cause of an increased stricture rate following the use of circular stapler is not known, but one may speculate that as the stapled anastomosis is deprived of a mucosa-to-mucosa apposition, the raw surface heals by second intention with granulation tissue formation. Wound inflammation and delayed epithelialization may then predispose to excessive fibrosis and stricture formation. In addition, the circumferentially placed metal staples do not allow the lumen to dilate beyond the size originally obtained and, predictably, the smaller the stapler size the greater the likelihood of eventual symptomatic stenosis.

The quality of hand-sewn anastomosis is influenced by the experience of the surgeon and the choice of technique. The continuous hand-sewn anastomosis used in this study is generally easy to perform. The technique largely overcomes the difficult placement of more than one layer of interrupted sutures at poorly accessible sites. Although anastomosis by the hand-sewn method using a single layer of continuous suture is not easy when carried out at the apex of the pleural cavity, it should be remembered that, when performing a stapled anastomosis, the purse string suture around the oesophagus has also to be inserted by hand.

The hand-sewn anastomosis allows mucosa-to-mucosa apposition. When minimal tension is applied, a continuous single layer suture offers coaptation with less risk of strangulating the intervening layers than a multilayered anastomosis in which overlapping sutures and infolding of tissues occur. Taking only the seromuscular layer of the substitute on the anterior wall ensures proper inversion without narrowing the lumen, and avoids compromising the precarious mucosal blood supply. With a comparable low leak rate between the hand-sewn method and circular staplers, the present results testify to the safety of a continuous single layer suture. In addition, there is a markedly reduced risk of stricture formation, a complication possibly minimized because the suture material is eventually absorbed which allows luminal expansion.

The suture material used may also be a contributing factor to the success of the continuous single layer anastomosis. Both Maxon and PDS are monofilament absorbable sutures which are relatively inert. They retain 50 per cent of their tensile strength for 4–5 weeks. These materials have favourable handling characteristics and good knot security and they are satisfactory for oesophageal anastomosis[20–22].

The present results also show that the incidence of leakage is the same in the neck as in the chest, and that a leak in the neck carries a similar risk of death to one in the chest (50 *versus* 27 per cent, respectively). This risk is not influenced by whether the anastomosis was performed by hand or by stapler. These results contradict the frequent claim that a cervical anastomotic leak is less lethal, and in many series the incidence of leakage in the neck is much higher than in the chest[23,24]. Another unsubstantiated claim is that a cervical anastomosis made after a more complete oesophagectomy (with a more generous resection margin) is associated with a lower incidence of anastomotic recurrence than a thoracic anastomosis[23]. This study has not demonstrated any difference in anastomotic recurrence rates between cervical and thoracic anastomoses, or between anastomoses made by hand or by stapler. The risk of recurrence is a function of resection margin[25] and we aim when feasible to obtain at least 5 cm of margin; this, in conjunction with the location of the tumour, determines the site of the anastomosis.

The very low incidence of leakage of the subsidiary anastomoses, one out of 245, further supports the safety of the single layer continuous hand-sewn technique for bowel anastomosis, a finding supported by others[26,27].

The results of the present non-randomized, non-controlled, study indicate that when performed adequately in selected patients, hand-sewn oesophageal anastomosis using a continuous layer of absorbable monofilament material is as effective as the use of a circular stapler. The former carries much less risk of stenosis and is less expensive. We recommend this technique of hand suture to surgeons with an interest in the surgery of oesophageal cancer.

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Results of fundoplication in a UK paediatric centre

**D. Parikh and
P. K. H. Tam**

*Institute of Child Health,
University of Liverpool, Liverpool,
UK*
Correspondence to:
Mr P. K. H. Tam, Nuffield
Department of Surgery,
John Radcliffe Hospital,
Oxford OX3 9DU, UK

Of 55 children (age 3 months to 16 years) who had fundoplication, major complications occurred in nine (16 per cent): paraoesophageal hernia (five cases), prolonged ileus (two cases), recurrent gastro-oesophageal reflux (one case), and accidental perforation (one case). The single most important factor resulting in complications was the omission of crural repair; of seven patients without crural repair, five developed paraoesophageal hernia/recurrence. Four patients required repeat fundoplication for severe recurrent symptoms and one of these developed the unusual complication of pericardiogastric fistula. Thirteen patients had strictures before operation from reflux oesophagitis, six (46 per cent) resolved after fundoplication alone, six responded to dilatation (mean five sessions), and one required colon interposition. Our preliminary experience with balloon dilatation was encouraging: three of three patients responded after one dilatation only. These results confirmed the efficacy of surgery in controlling reflux: 100 per cent in the short-term and 89 per cent on a 1–6 year follow-up. Major complications might well be reduced by routine crural repair.

Gastro-oesophageal reflux is a common problem in infancy and childhood, the initial treatment of which is medical. Surgery is reserved for those who fail to thrive or persistently vomit despite intensive medical therapy and for those who develop complications such as stricture formation and recurrent chest infection or apnoeic episodes. Antireflux surgery in children is usually effective but serious complications have also been reported[1–4]. Some complications are believed to be directly related to surgical techniques: inadequate mobilization of the oesophagus, improper wrap of stomach around the oesophagus, the omission of crural repair and the lack of anchorage of the gastric wrap to the undersurface of the diaphragm, have all been held to be responsible for the development of a paraoesophageal hernia and recurrent reflux[5]. It has also been suggested that particular groups of patients, such as those <2 years of age and those who have neurological impairment, are more prone to develop complications after fundoplication[6,7]. The types and incidence of complications of fundoplication in children vary from centre to centre. We therefore undertook a review of our results of fundoplication during the period 1983–1988 to address these issues.

Patients and methods

The hospital records of 55 infants and children who had fundoplication for the treatment of gastro-oesophageal reflux at the Royal Liverpool Children's Hospital Alder Hey in the period 1983–1988 were reviewed. Their ages ranged from 3 months to 16 years. The initial investigation was invariably a barium swallow and meal examination. Ambulatory 24-h oesophageal pH monitoring was carried out in 13 patients whose radiological studies were inconclusive. Oesophagoscopy and biopsy was performed on 24 patients who had symptoms of oesophagitis. The initial treatment was invariably medical comprising thickened feeds, posturing and Gaviscon® (Reckitt and Colman, Hull, UK); patients refractory to such treatment were given H_2-receptor antagonist in addition. The main indications for fundoplication are listed in *Table 1*. Most patients had gastrointestinal symptoms alone but 14 in addition had respiratory symptoms, of these 14 patients, seven had respiratory symptoms as the predominant problem while the remaining seven had both respiratory and gastrointestinal problems which contributed to the decision for operation. Of these 14 patients with respiratory problems, eight were neurologically impaired and two had had a previous repair of oesophageal atresia and tracheo-oesophageal fistula. All 55 patients had persistence of the presenting symptoms despite this intensive medical therapy for at least 1 month before a decision was made to operate.

Fundoplication was performed by one of five consultant paediatric surgeons or a surgical trainee under the supervision of a consultant. The operative approach was abdominal in 45 patients, thoracic in nine patients and abdominothoracic in one patient with severe kyphoscoliosis. All patients had oesophageal mobilization to ensure the presence of an intra-abdominal segment of oesophagus. The majority (54 patients) had a 360° floppy wrap of the fundus around the lower oesophagus (Nissen's procedure); one had a 270° wrap (Thal's procedure). Crural repair was carried out by placing two to three interrupted 3/0 silk sutures in the two limbs of the right crus of the diaphragm narrowing the oesophageal hiatus while still allowing the oesophagus with a wide-bore nasogastric tube *in situ* to pass through comfortably. The gastric wrap was anchored to the undersurface of the diaphragm by non-absorbable sutures in 21 patients. Pyloroplasty was not routinely performed: it was done in five patients, two of whom had radiological evidence of slow gastric emptying, one had a scarred pylorus and two had concomittant peptic ulcer (vagotomy was carried out simultaneously). Temporary gastrostomy was performed in only one patient who had oesophageal stricture for the purposes of feeding and Tucker's dilatation.

Fifty-one patients had regular follow-up to the present day; four patients had follow-up for 1 year only. Patients with recurrent symptoms and oesophageal stricture were reassessed with barium swallow examination and oesophagoscopy.

For statistical analysis χ^2 test was used and $P < 0.02$ was considered significant.

Results

The symptoms of gastro-oesophageal reflux were eliminated

Table 1 *Indications for fundoplication*

	No. of patients	(%)
Failure to thrive/persistent vomiting	28	(51)
Oesophageal stricture	13	(23)
Recurrent apnoeic episodes	2	(4)
Recurrent chest infection	5	(9)
Recurrent chest infection and vomiting	5	(9)
Recurrent chest infection and oesophagitis	2	(4)
Total	55	100

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Table 2 *Complications of fundoplication*

	No. of patients	(%)
Major complications	9	(16)
Paraoesophageal hernia	5	
Prolonged paralytic ileus	2	
Accidental gastric perforation	1	
Recurrent reflux	1	
Minor complications	4	(8)
Wound infection	1	
Incisional hernia	1	
Chest infection	1	
Stitch abscess	1	
No complications	42	(76)
Total	55	100

initially in all 55 patients after fundoplication. Six patients subsequently developed vomiting from complications discussed below.

There was no mortality. There were 13 complications (24 per cent): nine patients had major surgical complications of which five required reoperation (*Table 2*). The commonest major complication was paraoesophageal hernia: of five patients, four had persistent vomiting and radiological evidence of non-resolution/worsening of the hernia despite intensive medical therapy for more than 6 months before proceeding to operation. One patient had mild recurrent oesophageal reflux which was controlled by medication.

Prolonged paralytic ileus occurred in two patients and this resolved after 2 and 3 weeks respectively of non-operative management. To date no patient in this series has developed adhesive bowel obstruction.

Patients with severe kyphoscoliosis presented special technical problems for fundoplication. Of four such patients three had an abdominal approach and inadequate exposure in one of them resulted in accidental perforation of the stomach not recognized at the time of operation, the gastric perforation was subsequently repaired and the patient recovered uneventfully. One patient had an abdominothoracic approach and fundoplication was satisfactorily performed without complications.

Of four patients who had repeat fundoplication for significant paraoesophageal hernia, one developed the unusual postoperative complication of pericardiogastric fistula after a technically difficult re-operation: this child had a thoracotomy for the original fundoplication and during re-thoracotomy, extensive adhesions and a congenitally short oesophagus were found. Although there was no evidence of perforation of the stomach or pericardium at operation, ischaemic damage to either or both organs from operative trauma was deemed to be the likely cause for the subsequent development of a pericardiogastric fistula. The child was a Jeohvah's witness and major blood loss was not immediately replaced: this may have further contributed to the development of this complication. The fistula closed spontaneously after percutaneous drainage of the infected pericardal fluid collection, subsequent blood replacement and 6 weeks of total parenteral nutrition.

In this series, 16 children had moderate to severe neurological impairment (cerebral palsy, Arnold–Chiari malformation), three (19 per cent) of whom developed complications: paraoesophageal hernia (two cases), and recurrent gastro-oesophageal reflux (one case). The complication rate in this subgroup of patients was not different from the complication rate of the entire series ($P>0\cdot1$).

Of 55 patients, 19 were <2 years of age and two (11 per cent) developed complications (both had paraoesophageal hernia); this was not different from the complication rate of the entire series ($P>0\cdot1$).

Of 55 patients, 48 had crural repair and only one (2 per cent) developed paraoesophageal hernia; seven did not have crural repair and five (71 per cent) developed paraoesophageal hernia/recurrence ($P<0\cdot01$). Of 21 patients who had anchorage of the gastric wrap to the diaphragm, five (24 per cent) developed paraoesophageal hernia; in comparison, only one (3 per cent) of the 34 patients without wrap anchorage to diaphragm developed paraoesophageal hernia ($P>0\cdot02$). As all patients had oesophageal mobilization and the vast majority had the same form of fundoplication (Nissen's fundoplication, 54 cases; Thal's fundoplication, 1 case), the importance of oesophageal mobilization and the type of fundoplication in preventing the occurrence of paraoesophageal hernia or recurrence could not be assessed.

Oesophageal stricture from reflux oesophagitis was present in 13 patients before operation. In six patients the stricture resolved spontaneously after fundoplication alone (follow-up 1–4·5 years). Four patients had conventional bougeinage, of whom one responded to a single dilatation, two responded to more than three sessions of dilatation and the remaining patient failed to respond to 18 sessions of conventional Tucker's dilatation and required colon replacement Endoscopy-guided balloon dilatation was used for the treatment of the most recent three patients with oesophageal stricture and all three responded to one session of balloon dilatation (mean follow-up 8·6 months, range 6–12 months)

Discussion

The main indication for fundoplication in infants and children is the failure of medical treatment to control severe symptoms or complications of gastro-oesophageal reflux. Most infants with gastro-oesophageal reflux without a large hiatal hernia will respond to conservative treatment, the response rate in older children is lower[8] but still amounts to 80 per cent. It is, therefore, not surprising that the frequency of paedatric fundoplication is not high. In agreement with reports from UK and European centres[8,9] the majority of patients who required fundoplication had gastrointestinal problems, i.e. persistent vomiting, failure to thrive, oesophageal stricture and oesophagitis. Gastro-oesophageal reflux, however, can also give rise to respiratory complications including recurrent chest infection and apnoeic episodes (near-miss sudden infant death syndrome). In some American series, respiratory problem was the indication for fundoplication in up to 56 per cent of paediatric patients[4]; in contrast, a survey of European centres suggested that less than 5 per cent of paediatric fundoplication were done for respiratory reasons[8]. In our series, a respiratory problem was either the main reason or an important contributory factor for the decision to operate in 26 per cent of our patients The majority of our patients with respiratory problems were either neurologically impaired or had previous repair of oesophageal atresia, two conditions described to be associated with a high incidence of respiratory complications of gastro-oesophageal reflux[7,10]

Most repairs on the surgical treatment of gastro-oesophageal reflux in infants and children emphasized the satisfactory results of this procedure. In paediatric centres with extensive experience of fundoplication, symptomatic relief in over 95 per cent of patients, operative mortality rate of less than 0·8 per cent and operative morbidity rate of less than 8 per cent, have been achieved[11–13]. We were able to confirm the efficacy of surgery in controlling reflux: this was 100 per cent in the short-term and 89 per cent on follow-up of 1–6 years. We had no mortality. However, we encountered major complications in 16 per cent of our patients and this highlighted the fact that fundoplication in infants and children remained a major operative procedure.

Paraoesophageal hernia and recurrent gastro-oesophageal reflux were the commonest complications and their incidence in this series (11 per cent) was in general agreement with the reported incidence of 5·6–16·8 per cent from other series[5,6,14,15]. The occurrence of paraoesophageal hernia/ recurrent gastro-oesphageal reflux was likely to be related to the surgical technique employed. In our series, five of seven patients without crural repair (71 per cent) developed paraoesophageal hernia/recurrence whereas only one of 48 patients (2 per cent) with crural repair had this complication. Similar but less definite evidence was present in other reported series[14]. Infants and children with significant gastro-oesophageal reflux do not necessarily have an associated large hiatal hernia and in such circumstances the surgeon may decide that crural repair is not required. Mobilization of oesophagus intra-abdominally is, however, an essential step in fundoplication and a potential weakness in the hiatus may thus be created. We would recommend routine crural repair in fundoplication for infants and children.

We encountered prolonged paralytic ileus but did not experience any adhesive obstruction, a complication reported to occur in 5·1–10·3 per cent of patients in three series[5,16,17]. The absence of adhesive obstructive in our series was likely to be related to our low incidence of associated procedures (e.g. appendicectomy, gastrostomy, Ladds' procedure) performed during fundoplication. Minimal operative handling, however, should not mean inadequate surgical exposure as illustrated by our complication of accidental perforation of the stomach. Patients with severe kyphoscoliosis may present anatomical problems for fundoplication and in rare instances a thoracoabdominal approach may be necessary.

Although an increased incidence of complications has been noticed in children with neurological impairment and in children under 2 years of age in some series[6,7] we have not found either factor to affect our complication rate. We feel that the indications for antireflux surgery in these patients should not be different from those in the general paediatric population.

Our incidence of oesophageal stricture (23 per cent) in patients with gastro-oesophageal reflux who underwent fundoplication was similar to that in reported series[15] but should offer no complacency. With earlier referral and careful monitoring during initial medical treatment, reflux oesophagitis should not be allowed to proceed to stricture formation. Our experience showed that even when strictures had developed, effective antireflux treatment by surgery alone could result in spontaneous resolution of stricture in 46 per cent of cases. For strictures persisting after fundoplication, recurrent gastro-oesophageal reflux should be excluded by investigations including radiological and endoscopic assessment. Our initial experience with endoscopy-guided balloon dilatation[18] suggested that this procedure was superior to conventional bougienage for treating oesophageal stricture and resulted in eradication of strictures after one session of balloon dilatation in all three patients.

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Improving results in the treatment of gastric cancer: an 11-year audit

J. A. Akoh,
D. M. Sedgwick and
I. M. C. Macintyre

General Surgical Unit and Surgical Review Office, Western General Hospital, Edinburgh, UK
Correspondence to
Mr I. M C. Macintyre, Surgical Review Office, Alexander Donald Building, Western General Hospital, Edinburgh EH4 2XU, UK

Of 280 patients presenting to one hospital with gastric cancer between 1975 and 1985, 97 (35 per cent) did not undergo surgery and 29 per cent (54 out of 183) of those who did had no resection performed. The 30-day operative mortality rate in the study period was 15 per cent (28 out of 183) but in the subsequent 4-year period this fell to 7 per cent (5 out of 69). The survival rate correlated significantly with depth of invasion but not with tumour site or degree of differentiation. The incidence of early gastric cancer in this series was 5 per cent but the 5-year survival rate in this group was 52 per cent suggesting that the true incidence might be even lower. The overall 5-year survival rate in our area 20 years ago was only 5·2 per cent but in this series it was 11 per cent overall and 24 per cent after resection, and with actuarial correction 15 per cent overall and 28 per cent after resection. The continuing improvement in operative mortality rates and in 5-year survival rates gives grounds for optimism, but the disease must be diagnosed earlier if this improvement in outlook is to continue.

Although gastric cancer is perceived as a disease in decline, the workload presenting to general surgeons in the UK[1] and USA[2] has remained constant over the past 10 years It remains the fourth most common cause of death from malignant disease in Scotland[3]. The sense of optimism generated in Japan by the increase in early diagnosis and improved 5-year survival rate in the past 40 years[4,5] has not been felt elsewhere in the world. The generally held perception that gastric cancer is a disease that is diagnosed late, has a high operative mortality rate and 5-year survival rate of less than 10 per cent[6–8] has led to a nihilistic attitude towards treatment of the disease outside Japan.

In the present study all patients presenting to one hospital in an 11-year period have been examined to see if there has been any change in the operative mortality and 5-year survival rates that might encourage a less pessimistic attitude toward the disease

Patients and methods

All patients referred to the Western General Hospital, Edinburgh, between 1975 and 1985 were included Data were collected prospectively in the Gastric Follow-Up Clinic and Surgical Review Office[9,10] on a structured profoma and entered on to a computer database.

This information included biographical data, presenting features, treatment and outcome. Where an operation had been performed the extent of the resection was recorded. All biopsy and resected materials were examined histologically in the hospital's pathology department. To enable estimation of the proportion of patients with early gastric cancer, it has been assumed that all patients not coming to resection had disease more advanced than T_1

Survival curves were constructed by the life-table method described by Hill[11] and statistical comparison was made using the log rank test[12] Survival data are presented both in crude form and after actuarial correction. Information about the time and cause of death of each patient was obtained from the death certificate by arrangement with the Registrar General for Scotland. To assess trends in the operative mortality rate, the 30-day mortality rate in the study period was compared with that in the succeeding 4-year period

Results

All 280 patients with histologically confirmed carcinoma of the stomach were included in the study. The distribution by year of referral is shown in *Figure 1*. There were 169 men and 111 women (M·F ratio 1·5:1) and the overall median age was 68·1 years with a range of 33–96 years

Weight loss (45 per cent), abdominal pain (45 per cent), nausea/vomiting (40 per cent), anorexia (36 per cent) and dyspepsia (17 per cent) were the commonest presenting symptoms. The average duration of symptoms at presentation was 4·9 months. The 5-year survival rate for patients with duration of symptoms of 6 months or less was 12 per cent and for patients with duration of symptoms of more than 6 months was 17 per cent, but this difference was not statistically significant.

Ninety-seven (35 per cent) patients did not proceed to surgery (*Figure 2*). Of the 183 patients who underwent surgery 37 (20 per cent) had a biopsy only, 17 (9 per cent) had a bypass, and 129 (71 per cent) a resection. Of the 129 patients who underwent resection an oesophagogastrectomy or total gastrectomy was performed in 38 (29 per cent) and a distal gastrectomy was carried out in 91 (71 per cent) patients. The extended lymphadenectomy $(R_2/R_3)^{13,14}$ described by the Japanese was not performed in these patients. The 30-day operative mortality rate was 15 per cent (28 out of 183) overall and after resection was 13 per cent (17 out of 129).

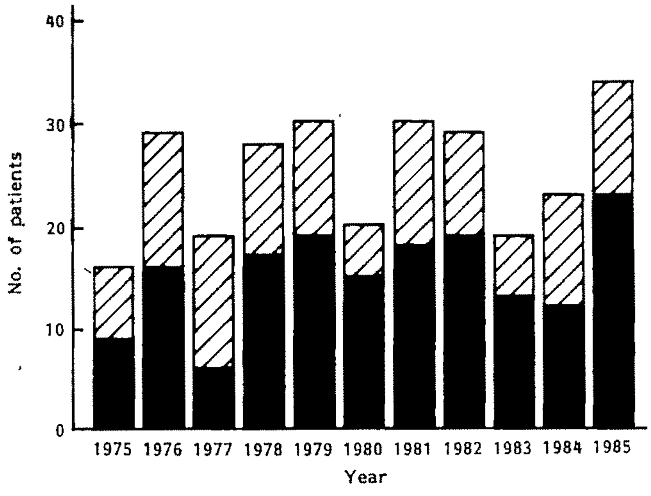

Figure 1 *Patients with gastric cancer referred to the Western General Hospital, Edinburgh between 1975 and 1985,* ■, *men,* ■, *women*

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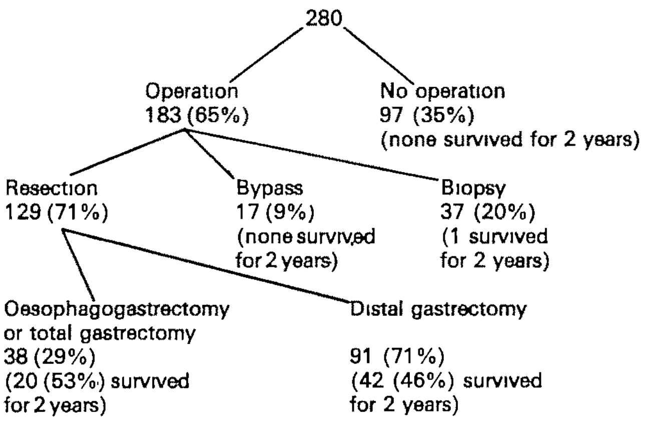
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Operation
183 (65%)
No operation
97 (35%)
(none survived for 2 years)
Resection
129 (71%)
Bypass
17 (9%)
(none survived for 2 years)
Biopsy
37 (20%)
(1 survived for 2 years)
Oesophagogastrectomy or total gastrectomy
38 (29%)
(20 (53%) survived for 2 years)
Distal gastrectomy
91 (71%)
(42 (46%) survived for 2 years)

Figure 2 *Treatment and outcome for 280 patients with gastric cancer*

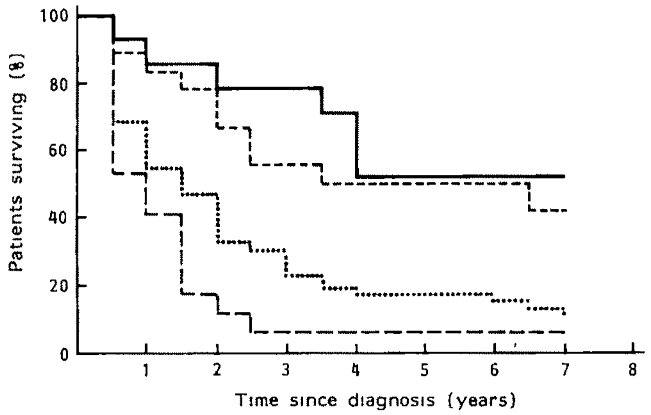

Figure 3 *Survival rates for patients with different depths of invasion of gastric cancer into the stomach wall, ——, mucosa and submucosa, ----, muscle; · · ·, serosa, ---, extragastric and fat,* P<0·001

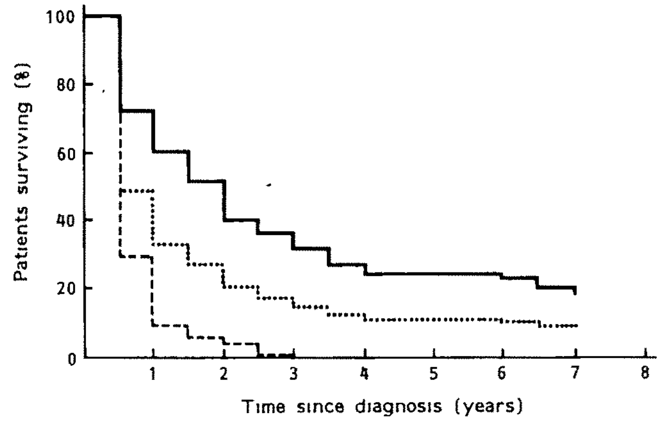

Figure 4 *Survival rates for all patients with gastric cancer (· ·), for those treated by resection (——) and those who had no resection (——),* P<0·001

The depth of invasion was assessed histologically in 128 of the 129 patients who underwent resection. Of these 14 (11 per cent) were T_1, 18 (14 per cent) were T_2, 79 (62 per cent) were T_3, and 17 (13 per cent) were T_4, i.e. only 5 per cent (14 out of 280) had early gastric cancer.

The survival rates for patients with well differentiated, moderately differentiated and anaplastic tumours did not show significant differences over 5 years. Tumour site did not influence survival. There was, however, a highly significant association between the depth of invasion into the stomach wall and survival rate (*Figure 3*).

None of the patients treated without operation survived 2 years and none of those treated by bypass survived 2 years. One of 37 patients treated by laparotomy and biopsy alone survived for 2 years without further adjuvant therapy (*Figure 4*). The life-table analysis shows that the overall 5-year survival rate was 11 per cent and the 5-year survival rate of patients undergoing resection was 24 per cent. Results showing actuarial correction applied to the survival data are shown in *Table 1*. This shows a 15 per cent overall 5-year survival rate and a 28 per cent 5-year survival rate for patients undergoing resection. The 5-year survival rate for patients with early gastric cancer becomes 66 per cent.

The operative mortality rate in the study period was compared with that in the subsequent 4-year period. During 1986–1989 the operative mortality rate had fallen to 7 per cent (five out of 69) after all operations and to 2 per cent (one out of 55) after resection

Discussion

For those seeking optimism in gastric cancer, this series has many pessimistic features. More than one-third of patients presenting did not proceed to operation, and in about one-third of those who did, resection was not performed. The resection rate did not increase over the study period. The number of patients presenting did not decline over the study period despite the well recognized decline in incidence rates. The reasons for this have been discussed elsewhere[1].

The study has again demonstrated a significant association between depth of invasion of the tumour and survival rate. The overall incidence of early gastric cancer in our series was 5 per cent. Our attempt to improve the diagnosis of early gastric cancer by an open access endoscopy service for general practitioners[15] did not result in an increase in the proportion of early gastric cancers being diagnosed. However, when this service is offered to all patients over the age of 40 years presenting with minor dyspeptic symptoms the rate of early gastric cancer can be as high at 15 per cent[16] and the survival rate is consequently improved.

Previous reports[17–19] have suggested that a history of symptoms of longer than 6 months is associated with a more favourable prognosis. The exact date of onset of the first symptom is frequently difficult and occasionally impossible to establish even when the data are collected prospectively The present study failed to show such an association.

The 5-year survival rate of stage 1 cancers in this series (52 per cent) is lower than the 72 per cent reported from the West Midlands[7] and the 98 per cent reported for this group of patients in Japan[4,20]. The recent report into early gastric cancer by the British Society of Gastroenterology[21] has also shown a greater than 90 per cent 5-year survival rate for early gastric cancer in the UK. However, 22·5 per cent of patients said by referring pathologists to have early gastric cancer were reclassified by an 'expert' panel as having more advanced disease. The 4-year survival rate for this latter group was less than 70 per cent. This suggests that many gastric cancers reported by hospital pathologists as 'early' could in fact be more advanced disease. Given that the numbers of early gastric cancers are small, the inclusion of even a few advanced cases will greatly alter the apparent survival data. It seems likely therefore that the true incidence of early gastric cancer in our

Table 1 *Survival rates after actuarial correction*

Time after diagnosis/operation (years)	Percentage surviving		
	Resection	No resection	All
1	63	10	34
2	44	4	22
3	36	0	17
4	29	–	15
5	28	–	15

Table 2 *Gastric cancer operative mortality rates*

Reference	Year	No. of patients	Operative mortality rate (%)
Hoerr[23]	1973	478	10·2
Lundh *et al.*[8]	1974	901	23
McNeer *et al*[24]	1974	534	17·8
Zacho *et al.*[25]	1974	776	(11·3)
White *et al*[17]	1975	242	7·1
Inberg *et al.*[26]	1975	2590	(10·5)
Cassell and Robinson[27]	1976	854	16·2
Dupont *et al.*[28]	1978	1497	26·5
Peters[29]	1982	304	(14·8)
Papachristou and Fortner[30]	1982	112	(12·5)
Yap *et al.*[31]	1982	465	(2·8)
Bizer[32]	1983	171	13·7
Paolini *et al.*[33]	1986	110	(18)
Irvin and Bridger[34]	1988	122	9
Allum *et al*[7]	1989	31 567	26·9
Meyer *et al*[35]	1989	1510	(12·4)
Parker (unpublished results)	1990	1651	20·7
Present study	1991	280	15·3 (13·2)

Figures in parentheses refer to resected cases only

series was even lower than 5 per cent. This may not be the entire explanation for the differences between Japan and the West. Some authors, including Fielding[20], believe that the difference in survival figures for the same stage of disease is due to difference in biological behaviour.

The overall 5-year survival rate reported 20 years ago from our region was 5·2 per cent[22]. Although a smaller proportion of patients in the present series came to resection (suggesting improving selection), the 5-year survival was more than double at 11 per cent Furthermore the 1-year survival rate following resection was 73 per cent compared with 24 per cent in the 1971 series.

The operative mortality rate in this series was high following resection (13 per cent) but compared favourably with rates published by other Western centres over the past 20 years (*Table 2*). There is more cause for optimism about improved outlook in the operative mortality rate in the subsequent 4-year period in our hospital. Following resection the operative mortality rate is now only 2 per cent and other non-Japanese series[31,34,36] have also shown that figures similar to this are possible.

The effects on 5-year survival rate of the R_2/R_3 resection, which we have practised since 1985, remain to be seen. When added to the improved operative mortality rate, this will, we anticipate, give even greater cause for optimism in this disease.

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Non-ominous micrometastases of gastric cancer

P. Gunvén,
K. Maruyama,
K. Okabayashi,
M. Sasako and
T. Kinoshita

Division of Gastric Surgery, National Cancer Center Hospital, Tokyo, Japan
Correspondence to:
Dr P. Gunvén, The Gastrointestinal Tumour Service, Department of Surgery, Karolinska Hospital, PO Box 60500, S-104 01 Stockholm, Sweden

So-called R_2 or wider meticulous node dissection was performed in 1368 patients with resected gastric cancer invading beyond the submucosa but without distant metastases. Survival rates were similar in subsets of patients with or without microscopic node metastases and macroscopically normal lymph nodes. The extent of node metastases has previously been shown to be one of the two most important prognostic factors in gastric cancer without distant metastases, and its lack of impact in these patient groups was not explained by the imbalance of other prognostic factors. The findings indicate that micrometastases of gastric cancer are curable by a wide node dissection made in the absence of palpable abnormality. They also offer the possibility that an extensive node dissection may yield good stage-specific survival rates, in part because of upstaging of patients. The findings should influence the recording of node metastases for evaluation of stage-specific treatment results and for research purposes.

Japanese surgeons report favourable stage-specific survival rates after operations for gastric cancer. The results have been ascribed to a meticulous lymph node dissection and/or to a hypothetically less aggressive form of the disease in Japan. Owing to the wide consensus in Japan on the desirability of lymph node dissection, randomized studies to evaluate its role are not feasible in that country. Therefore, one cannot test the hypothesis that such node dissection gives better survival figures because of an upstaging by detection of more metastases, even if it has no therapeutic effect.

Small metastases are those likely to be detected after routine dissection of macroscopically normal nodes. If they have limited prognostic significance, as in breast cancer[1], patients with such metastases (and lower than average survival rates in the stage defined by conventional dissection) could be assigned to a higher stage after meticulous dissection. Even if the dissection had no therapeutic effect, the prognosis of these patients may be better than the average for their new stage. This stage migration phenomenon[2] would improve the prognosis in both stages.

Randomized studies of conventional compared with extended node dissection in the Western world[3] may be limited by the relative rarity of the disease and a lack of familiarity with the technique of node dissection. Subsets of patients who may benefit from node dissection, e.g. those with limited extent of node metastases, may be small and the recording of node status insufficiently detailed.

During an analysis of lymph node metastases in gastric cancer, it was found that macroscopically unrecognized lymph node deposits did not have a negative impact on survival as long as they were removed by an extended node dissection. These findings may have relevance for decisions on operative strategies and for staging of stomach cancer.

Patients and methods

Resection was carried out in 1368 patients with gastric cancer invading beyond the submucosa, but without gross distant spread to the liver or peritoneum, between 1974 and 1988 using a so-called R_2 or more extensive node dissection. The male to female ratio was 2:1 and the mean(s.e.m.) age 58(12) years. The standardized node dissection[4,5] removed at least two of the four large groups or tiers of the 16 upper abdominal lymph node stations, as defined in Japan[4]. These stations and tiers are described in *Table 1*. The tiers are numbered according to their anatomical relation to the tumour Their extent and that of the R_2 dissection, that removes the two tiers closest to the tumour, therefore vary depending on the location of the tumour[4] Very few of the resections required blood transfusion, an event that did not affect stage-specific survival rates in our patients[6].

The resected specimen was meticulously dissected and an average of more than 30 individual nodes identified and evaluated macroscopically by size, shape and firmness N_0 denoted normal findings and N_+ suspected metastases. Each node was examined histopathologically and the findings were recorded as negative (n_0) or positive with extension to an indicated tier of nodes (n_{1-3}). Cumulative survival rates including operative mortality with Greenwood's 5 per cent standard error were calculated[7] for subsets of patients categorized by macro- (N) and microscopic (n) findings The patients were subgrouped according to macro- and microscopic node status. These subsets did not differ significantly from each other with regard to sex ratio or mean age. Less than 4 per cent of the patients were lost to follow-up, with less than 6 per cent lost in any subset.

Results

The patients were grouped according to macro- and microscopic node status and the subsets with macroscopically normal nodes without (N_0n_0) and with node micrometastases

Table 1 *Numbering and grouping of upper abdominal lymph node stations*

		Tier no. for tumour in		
Station	Location	A, AM	M, MA, MC	C, CM
1/2	Right/left side of cardia	2/3	1/2	1
3/4	Lesser/greater curvature	1	1	1
5/6	Supra/infrapyloric	1	1	2
7	Left gastric artery	2	2	2
8	Common hepatic artery	2	2	2
9	Coeliac artery	2	2	2
10/11	Splenic hilum/artery	3	2	2
12/13	Hepatoduodenal ligament/behind pancreas head	3	3	3
14	Root of superior mesenteric artery	3	3	3
15	Middle colic artery	4	4	4
16	Para-aortal	4	4	4

C, M, A, proximal (cardiac), middle, distal (antral) thirds of stomach; main area involved given first in the combinations R_2 dissection includes all node stations in the first and second tiers

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Table 2 *Characteristics of groups of patients with gastric cancer with different extent of node involvement*

Node status	No. of patients	Percentage of patients with							
		Microscopic serosal invasion				Upper third tumour	Scirrhous cancer	Total gastrectomy	Palliative resection
		s_0	s_1	s_2	s_3				
N_0 n_0	228	70	11	18	1	20	4	27	1
n_1	77	65	20	13	3	14	3	20	0
n_2	59	56	22	22	0	22	3	22	2
N_+ n_0	192	34	13	39	15	29	10	46	2
All	1368	37	11	38	15	24	10	41	6

$N_{0/+}$, macroscopically normal/metastatic nodes; $n_{0/1/2}$, histologically metastatic nodes absent/in tier 1/in tiers 1 and 2; s_0, none; s_1, suspected; s_2, definite, s_3, invasion of neighbouring organs

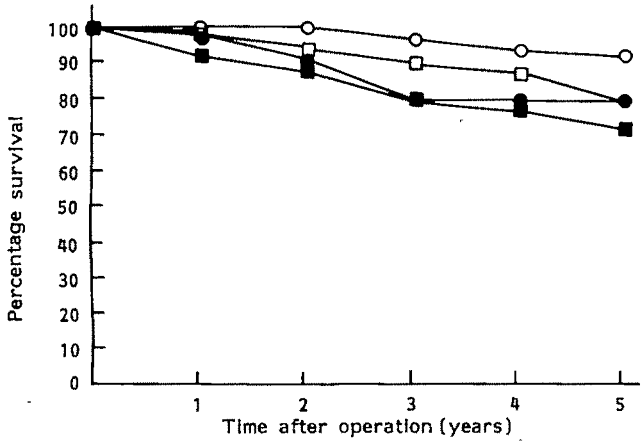

Figure 1 *Crude cumulative survival rates according to Kaplan–Meier for subsets of patients with resected gastric cancer.* ○, *N_0n_1;* □, *N_0n_0,* ●, *N_0n_2,* ■, *N_+n_0. Macroscopically uninvolved (N_0) or supposedly metastatic (N_+) lymph nodes were related to the microscopic extent of spread. n_0, none, n_1, to the first tier of regional nodes, n_2, to the first and second tiers No significant differences were found*

to the first or first and second tiers (N_0n_1 and N_0n_2) were compared with each other and with the subset of patients with macroscopically suspect but microscopically uninvolved nodes (N_+n_0). The incidence of prognostically unfavourable factors (serosal invasion, proximal tumours and scirrhous cancers[8]) were similar in the subsets, as were the frequencies of total gastrectomies and palliative resections (*Table 2*).

The cumulative crude 5-year survival rates, including operative mortality rate, were 55 per cent for all 1368 resected patients, 74 per cent for 420 histologically node negative (n_0) patients, and 47 per cent for 948 n_+ patients. The subset of 192 N_+n_0 patients had a survival rate of 70 per cent.

The survival rates of the various subsets of patients are shown in *Figure 1*. Only two patients were macroscopically normal in the presence of micrometastases to the third tier of nodes, i.e. N_0n_3; one of them survived for 5 years (this subset not shown in *Figure 1*).

Depth of tumour invasion and extent of node metastases were outstandingly the two most important prognostic factors in the absence of distant metastases, each with a ratio of risk for death of more than 4 according to Cox' proportional hazard model in a previous analysis of our patients[8]. We therefore separated subgroups of patients without microscopic serosal invasion, 160 in the category N_0n_0 and 50 in N_0n_1, that had mean(s.e.m.) 5-year survival rates of 85(6) and 94(8) per cent respectively. We also recorded the extent of microscopic serosal invasion as well as two other unfavourable prognostic factors, the proportions of Borrman type 4 tumours (scirrhous cancers; ratio of risk 1·8)[8], and of cancers in the upper third of the stomach (ratio of risk 1·5) for the various Nn categories. The proportions of total gastrectomies and palliative resections were also recorded (*Table 2*). No striking differences between the groups were observed and their survival rates did not differ significantly despite the variations in the extent of node metastases.

Discussion

The finding that macroscopically unrecognized lymph node metastases of gastric cancer did not influence the prognosis strikingly was made during an analysis of the significance of node metastases in this disease[9], and could be made owing to a routine wide removal of macroscopically normal nodes.

The number of nodes in each specimen was similar to that obtained by chemical clearing of gastrectomy specimens[10,11], supporting the validity of the analysis. They were evaluated macroscopically in fresh-resected specimens, i.e. under more favourable conditions than those during operation. In view of this, we suggest that a standardized extended dissection should be performed in the absence of palpable metastases, until analyses of incidence and curability of node metastases in the various node stations for tumours with different locations and depths of invasion have been made to guide the dissection in individual cases. The recording of findings was not designed to answer questions such as 'what size of deposits has prognostic significance?' or 'which macroscopic criterion of disease, size, shape or firmness is most reliable?'

It was concluded that macroscopically unrecognized node metastases lacked prognostic significance after a comparison of subgroups within a homogeneous patient group, operated on using a strictly standardized technique by a few surgeons experienced in stomach cancer. There were no differences among other known important prognostic variables than the extent of node deposits that could possibly have masked any survival advantage of N_0n_0 patients over N_0n_{1-2} patients. On the contrary, the N_0n_0 group contained fewer patients with prognostically unfavourable serosal invasion. The inclusion criterion of an R_2 or more extensive resection and exclusion of patients with liver or peritoneal seeding favoured resections for cure, and this bias was intended to remove confounding prognostic factors. The findings support the theory that small node metastases of gastric cancer can be cured surgically; they are probably early events in an orderly spread along defined lymphatic channels[9].

However, if such deposits are believed to be indolent or dormant, one may speculate that an upstaging mechanism may at least in part explain the claimed superiority of extended node dissection in gastric cancer. Further randomized studies, such as are underway in the UK and The Netherlands, of limited compared with extensive node dissection are needed to clarify such points Recording the sizes of individual node deposits is recommended to investigate the importance of this variable; the recording of node metastases for use in international comparisons of stage-specific survival rates should be standardized.

Acknowledgements

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POSSUM: a scoring system for surgical audit

G. P. Copeland, D. Jones and M. Walters

Department of Surgery, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB, UK
Correspondence to:
Mr G P Copeland

POSSUM, a Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity, is described. This system has been devised from both a retrospective and prospective analysis and the present paper attempts to validate it prospectively. Logistic regression analysis yielded statistically significant equations for both mortality and morbidity ($P < 0.001$). *When displayed graphically zones of increasing morbidity and mortality rates could be defined which could be of value in surgical audit. The scoring system produced assessments for morbidity and mortality rates which did not significantly differ from observed rates.*

While data regarding the access of patients to care and outcome (presented as overall mortality and morbidity rates) are relatively easy to derive, 'quality of care' has proved a more elusive determinant. In most hospitals, quality of care is assessed by discussion of individual cases or by review of series of patients undergoing particular types of surgical procedure. Comparisons between different surgeons, units, hospitals and regions are bedevilled by differences in patient presentation, general fitness of the local populace and the nature of the surgery undertaken.

The Royal College of Surgeons of England has defined audit as the 'systematic appraisal of the implementation and outcome of any process in the context of prescribed targets and standards'[1]. The difficulty in this definition rests in the interpretation of prescribed targets and standards, and it infers that outcome for individuals and series of patients can be predicted In this context morbidity is probably as important as mortality, certainly when discussing quality of care. Perhaps of parallel importance in audit is the discussion of individuals in whom death or complications could have been expected, but did not occur. Thus audit should include discussion of 'surgical success', in addition to mortality and morbidity rates, if it is to be educational.

The ideal scoring system for surgical audit purposes should assess mortality and morbidity and should allow audit retrieval of the surgical success. It should be quick and easy to use and should be applicable to all general surgical procedures in both the emergency and elective setting It should be of use in all types of hospital and should provide educational information. Finally it should be possible to integrate the scoring system into pre-existing audit programmes with the minimum of disruption.

There are many scoring systems that predict the risk of mortality with varying degrees of accuracy. However, morbidity is almost universally ignored. Many scores have been devised which are ideally suited to special types of surgical procedure or to assessing particular types of complication. Some scores are ideal for assessing the risk of mortality and to a lesser extent morbidity in particular groups of surgical patients, such as those with cardiovascular[2,3] and gastrointestinal[4–8] disease, or for assessing the risk of developing particular complications[9,10]. Others are of use in particular surgical settings, such as patients requiring intensive care[11,12]. Probably the best known and most widely used scoring system is APACHE II which is ideal for the intensive care patient but requires 24 h of observation and weighting tables for individual disease states[12]. Whereas such a score can be applied to the majority of general surgical patients it only assesses the risk of mortality. Theoretically the smaller the number of variables the easier the scoring system. Indeed some systems have reduced the number of variables to two (age and lymphocyte count[13]) but this reduction clearly has disadvantages if one factor is not available. Other scoring systems have reduced variables by multifactorial analysis and have derived complex mathematical equations to assess the risk of mortality, but few surgeons carry calculators in everyday practice.

We identified the need for a simple scoring system that could be used across the general surgical spectrum, whose main use would be in surgical audit. Our present system has been in development over the past 2 years. Initially 62 individual factors (48 preoperative factors and 14 operative and postoperative factors) were assessed by a multivariate discriminant retrospective analysis over a 6-month period, to reduce the number of variables. Of these, 35 factors were assessed prospectively for a further 6 months to produce the present scoring system. In this later prospective analysis all variables were subjected to multivariate discriminant analysis and, using this linear discriminant technique[14], multivariate discriminant function coefficients were obtained for each set of variables Only significant independent factors were included in the final score design. The multivariate discriminant function coefficients of those remaining factors were divided by a constant and rounded to the nearest whole number to derive a point value on an exponential score (1, 2, 4, 8) for the variable Thus a 12-factor, four-grade, physiological score was developed. Any decrease in score variables below this level resulted in a loss of predictive ability for mortality or morbidity While this preoperative physiological score yields a statistically predictive risk of morbidity and mortality for the patients overall, there were intergroup differences depending on the nature of the surgical procedure. Logistic regression analysis of all data enabled a six-factor, surgical, operative severity score to be evolved which compensated for the type of surgical procedure.

In the present prospective study we have applied this dual scoring system to all patients admitted during a 6-month period, equivalent to our periods of previous study During this period the present POSSUM (*P*hysiological and *O*perative *S*everity *S*core for the en*U*meration of *M*ortality and morbidity) system has been assessed.

Patients and methods

During the 6 months from August 1988 to February 1989 all patients admitted for inpatient surgery were scored using the POSSUM system at Walton Hospital, Liverpool. In all, 1440 patients underwent elective or emergency surgery during this period and required inpatient care for at least 24 h after operation. Patients undergoing surgery for trauma (12 patients) and those in whom no outpatient review at 6 weeks was available (56 patients) were excluded. Thus 1372 prospectively scored patients were available for study

All patients were scored before operation (using the physiological score) and at discharge (using the operative severity score) The physiological score reflects the indices at the time of surgery rather than at the time of admission. All patients had blood samples taken for determination of urea and electrolyte levels, haemoglobin concentration

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Table 1 *Physiological score (to be scored at the time of surgery)*

	Score			
	1	2	4	8
Age (years)	≤60	61–70	≥71	
Cardiac signs	No failure	Diuretic, digoxin, antianginal or hypertensive therapy	Peripheral oedema; warfarin therapy	Raised jugular venous pressure
Chest radiograph			Borderline cardiomegaly	Cardiomegaly
Respiratory history	No dyspnoea	Dyspnoea on exertion	Limiting dyspnoea (one flight)	Dyspnoea at rest (rate ≥30/min)
Chest radiograph		Mild COAD	Moderate COAD	Fibrosis or consolidation
Blood pressure (systolic) (mmHg)	110–130	131–170 100–109	≥171 90–99	– ≤89
Pulse (beats/min)	50–80	81–100 40–49	101–120	≥121 ≤39
Glasgow coma score	15	12–14	9–11	≤8
Haemoglobin (g/100 ml)	13–16	11·5–12·9 16·1–17·0	10·0–11·4 17·1–18·0	≤9·9 ≥18·1
White cell count ($\times 10^{12}$/l)	4–10	10·1–20·0 3·1–4·0	≥20·1 ≤3·0	
Urea (mmol/l)	≤7·5	7·6–10·0	10·1–15·0	≥15·1
Sodium (mmol/l)	≥136	131–135	126–130	≤125
Potassium (mmol/l)	3·5–5·0	3·2–3·4 5·1–5·3	2·9–3·1 5·4–5·9	≤2·8 ≥6·0
Electrocardiogram	Normal		Atrial fibrillation (rate 60–90)	Any other abnormal rhythm or ≥5 ectopics/min Q waves or ST/T wave changes

COAD, chronic obstructive airways disease

Table 2 *Operative severity score. (Definitions of surgical procedures with regard to severity are guidelines; not all procedures are listed and the closest should be selected)*

	Score			
	1	2	4	8
Operative severity*	Minor	Moderate	Major	Major+
Multiple procedures	1		2	>2
Total blood loss (ml)	≤100	101–500	501–999	≥1000
Peritoneal soiling	None	Minor (serous fluid)	Local pus	Free bowel content, pus or blood
Presence of malignancy	None	Primary only	Nodal metastases	Distant metastases
Mode of surgery	Elective		Emergency resuscitation of >2 h possible† Operation <24 h after admission	Emergency (immediate surgery <2 h needed)

* Surgery of moderate severity includes appendicectomy, cholecystectomy, mastectomy, transurethral resection of prostate; major surgery includes any laparotomy, bowel resection, cholecystectomy with choledochotomy, peripheral vascular procedure or major amputation; major+ surgery includes any aortic procedure, abdominoperineal resection, pancreatic or liver resection, oesophagogastrectomy; † indicates that resuscitation is possible even if this period is not actually utilized

and white cell count, and all had electrocardiography performed. A chest radiograph was obtained in 69·7 per cent of patients.

Scores were awarded according to *Tables 1* and *2*. Complications were recorded on a separate sheet (*Table 3*).

For the purposes of study the following definitions were used:

Wound haemorrhage. local haematoma requiring evacuation

Deep haemorrhage postoperative bleeding requiring re-exploration

Chest infection· production of purulent sputum with positive bacteriological cultures, with or without chest radiography changes or pyrexia, or consolidation seen on chest radiograph

Wound infection: wound cellulitis or the discharge of purulent exudate

Urinary infection· the presence of >10^5 bacteria/ml with the presence of white cells in the urine, in previously clear urine

Deep infection: the presence of an intra-abdominal collection confirmed clinically or radiologically

Septicaemia· positive blood culture

Pyrexia of unknown origin· any temperature above 37°C for more than 24 h occurring after the original pyrexia following surgery (if present) had settled, for which no obvious cause could be found

Wound dehiscence· superficial or deep wound breakdown

Deep venous thrombosis and pulmonary embolus: when suspected, confirmed radiologically by venography or ventilation/perfusion scanning, or diagnosed at post mortem

Cardiac failure. symptoms or signs of left ventricular or congestive cardiac failure which required an alteration from preoperative therapeutic measures

Impaired renal function arbitrarily defined as an increase in blood urea of >5 mmol/l from preoperative levels

Hypotension: a fall in systolic blood pressure below 90 mmHg for more than 2 h as determined by sphygmomanometry or arterial pressure transducer measurement

Table 3 *Information to be included on a complications record sheet*

- Name
- Hospital no.
- Diagnosis
- Operation
- Date of admission
- Date of operation
- Date of discharge
- Surgeon
- Anaesthetist
- Outcome*
  - Haemorrhage
    - Wound
    - Deep
    - Other
  - Infection†
    - Chest
    - Wound
    - Urinary tract
    - Deep
    - Septicaemia
    - Pyrexia of unknown origin
    - Other
  - Wound dehiscence
    - Superficial
    - Deep
  - Anastomotic leak
  - Thrombosis
    - Deep vein thrombosis
    - Pulmonary embolus
    - Other
    - Cerebrovascular accident
    - Myocardial infarct
  - Cardiac failure
  - Impaired renal function (urea increase >5 mmol/l from preoperative level)
  - Hypotension (<90 mmHg for 2 h)
  - Respiratory failure
  - Any other complication
  - In the event of death give date
  - Post-mortem findings

* Give dates for all complications; † for infection give bacteria cultured if known

Respiratory failure respiratory difficulty requiring emergency ventilation
Anastomotic leak· discharge of bowel content via the drain, wound or abnormal orifice.

Many of these complications have been arbitrarily set for the purposes of this study, and were assessed and recorded by one of the three authors in all cases. Complications were assessed by clinical observation. Routine bacteriological screening and postoperative radiological scanning were not carried out, but confirmatory bacteriological and radiological tests were carried out where clinical suspicion existed.

Method of analysis

Using outcome (dead/alive or complicated/uncomplicated) as a dichotomous dependent variable, we have derived multiple logistic regression equations for both morbidity and mortality. Significance was assessed using model χ^2.

Differences between observed and expected outcomes were assessed using χ^2 tests.

Results

The types of surgical procedure performed are illustrated in *Table 4*. The overall mortality rate was 4·0 per cent and the overall morbidity rate was 16·6 per cent. The range of physiological scores obtained is shown in *Figure 1* and that of operative severity scores can be seen in *Figure 2*.

Logistic regression analysis yielded statistically significant equations for both morbidity and mortality For morbidity this was $\ln R/1-R = -5{\cdot}91 + (0{\cdot}16 \times \text{physiological score}) + (0{\cdot}19 \times \text{operative severity score})$ ($P<0{\cdot}001$). For mortality this was $\ln R/1-R = -7{\cdot}04 + (0{\cdot}13 \times \text{physiological score}) + (0{\cdot}16 \times \text{operative severity score})$ ($P<0{\cdot}001$). Using the physiological score as the x axis and the operative severity score as the y axis it was possible from these equations to generate graphically zones of increasing mortality (*Figure 3*) and morbidity (*Figure 4*) rates.

The predictive accuracy of these equations was assessed by the determination of receiver operating characteristic curves (ROC curves), by determining classification matrices for

Table 4 *Types of surgical procedure performed in the 1372 assessed patients (833 elective and 539 emergency procedures)*

	No. of procedures
Vascular procedures	101
Gastrointestinal procedures	432
Hepatobiliary	120
Urological	105
Miscellaneous	614

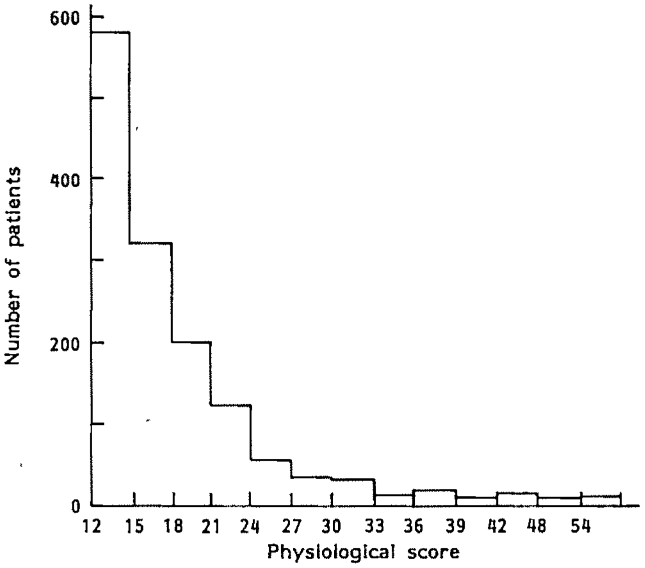

Figure 1 *Distribution of patients with regard to physiological score Each bar represents the number of patients in that score range*

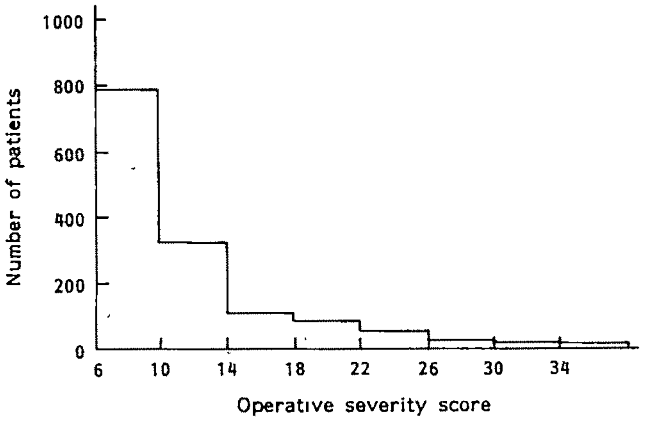

Figure 2 *Distribution of patients with regard to operative severity score Each bar represents the number of patients in that score range*

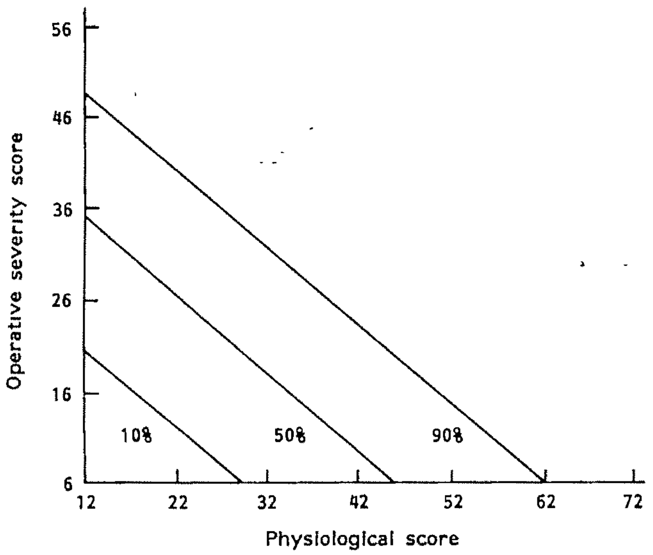

Figure 3 *Zones of increasing mortality rate derived from the logistic regression analysis*

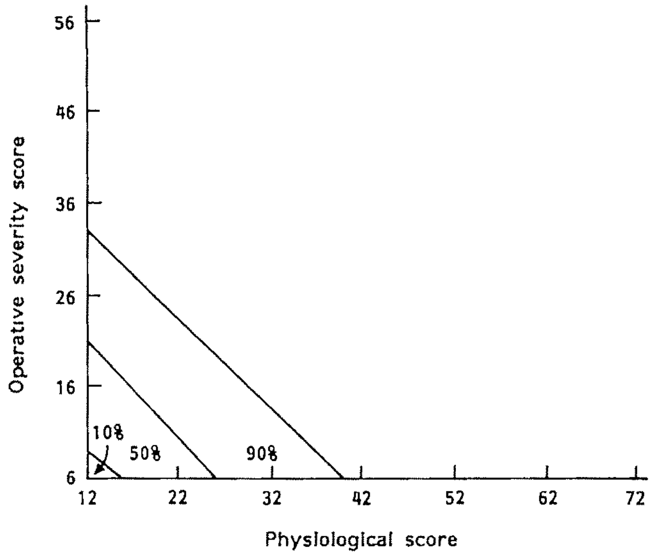

Figure 4 *Zones of increasing morbidity rate derived from the logistic regression analysis*

Table 5 *Classification matrix of 50 per cent predicted risk of death (predictions are derived from the logistic equation)*

	Status		
	Alive	Dead	Total
Alive	1278	39	1317
Dead	9	46	55
Total	1287	85	1372

Negative predictive value, 83·6 per cent, positive predictive value, 97·0 per cent, specificity, 99·3 per cent, sensitivity, 54·1 per cent; total correct classification, 96·5 per cent

different levels of predicted mortality and morbidity. Such a matrix for the 50 per cent prediction of risk of mortality is shown in *Table 5* and for risk of morbidity is shown in *Table 6*. The resultant ROC curves are illustrated in *Figures 5* and *6*.

The comparison between predicted and observed rates of morbidity and mortality expressed numerically are illustrated in *Table 7*.

Discussion

Surgical audit has increased in importance over the past few years, both as an educational process and as a means of assessing the quality of surgical care. We felt that a need existed to allow assessment of the 'quality' of care, but to do so it must

Table 6 *Classification matrix of 50 per cent predicted risk of complication resulting from surgery (predictions are derived from the appropriate logistic equation)*

	Status		
	Uncomplicated	Complicated	Total
Uncomplicated	1021	123	1144
Complicated	94	134	228
Total	1115	257	1372

Negative predictive value, 58·8 per cent; positive predictive value, 89·2 per cent, specificity, 92·4 per cent; sensitivity, 52·1 per cent; total correct classification, 84·2 per cent

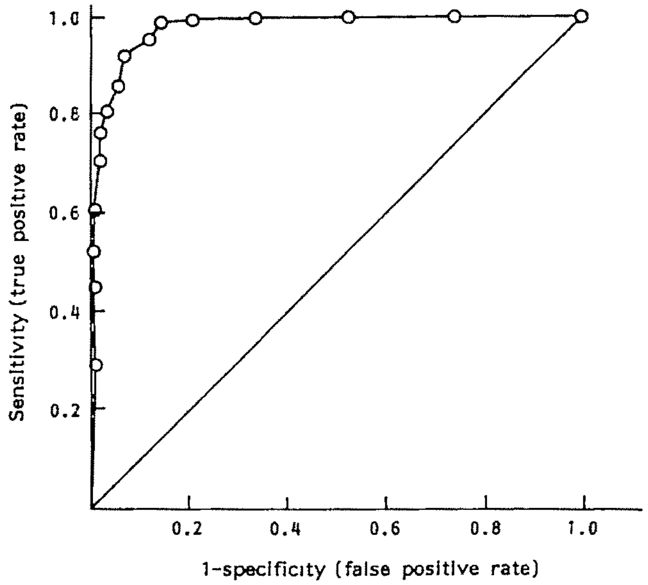

Figure 5 *Receiver operating characteristic curve for mortality*

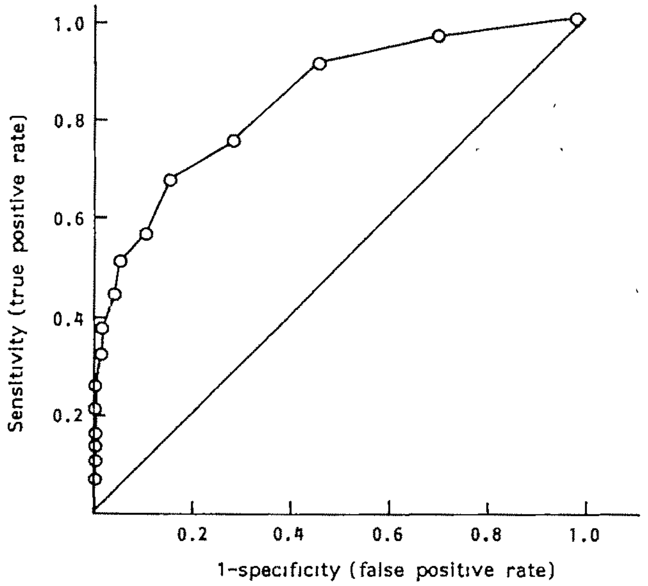

Figure 6 *Receiver operating characteristic curve for morbidity*

Table 7 *Predicted* versus *observed rates for mortality and morbidity**

Predicted risk (%)	Observed rate (%)	
	Mortality	Morbidity
85	86·5	84·3
75	78·3	75·7
65	67·7	67 3
55	56·4	56·9
45	46·0	47 5
35	38·5	37·4
25	29·3	26·4

* There was good correlation between observed and predicted rates for morbidity and mortality ($P<0\,001$)

be possible to set norms for any particular surgical procedure and to allow its comparison with other dissimilar procedures. Scoring would seem to be the best method available for assessing the risk of mortality and morbidity, but existing scoring systems did not completely meet our expectations as being readily applicable to audit. One worrying feature of scores that estimate the risk of mortality and morbidity preoperatively, or in the immediate perioperative stage, was that they could be used to decide on the continuance of resuscitative measures. Our intention was to develop a score to aid audit and we therefore devised a method in which the full score, and the numerical estimate of risk of mortality and morbidity, was not available until outcome was known; in this way we hoped to minimize the risk of inappropriate score usage.

The physiological score variables and individual factor weightings were devised by a linear multivariant discriminant technique which has been recommended as the statistical method that best simulates the formation of clinical judgement[14]. A similar technique has been used by others to assess risk factors[10]. The information obtained from this analysis was combined with both linear discriminant and logistic regression analysis to produce the present physiological and operative severity score. We attempted to devise a scoring system applicable to all general surgical patients in all surgical settings. The present scores were developed from the clinically observed mortality and morbidity rates, rather than fitting the score to the data by the application of weighting tables. The present score is both quick and easy to use. The clinical features scored are all assessed as part of the usual admitting clinical history and examination, and all the biochemical, radiological and cardiological investigations are readily available in all clinical settings. This means that, with practice, both scores can be gauged within 3 min by all grades of staff. In 50 patients scored by three different individuals there was complete agreement in 47 cases. In the remaining three cases there was variation in score in only four different variables (but this did not adversely affect the score's usefulness).

Complications were assessed by observation. While this means that some subclinical complications may have been missed, we felt that these would be unlikely to be of clinical significance, especially as we had adopted a 6-week follow-up period.

To be of use in surgical audit the scoring system must produce a valid assessment of the risk of mortality and morbidity. That the present scoring system achieves these aims is well demonstrated by the ROC curves obtained for mortality and morbidity and by comparing the actual rates *versus* predicted rates (*Figures 5* and *6; Table 7*) for these two parameters. It should be stressed that the assessment obtained for a particular score combination relates to a group of patients with that particular score combination rather than an individual. Certainly, with regard to patients undergoing vascular and gastrointestinal procedures, no additional weighting to the logistic regression equation is required to improve its statistical predictive ability for morbidity and mortality. The mortality rate for patients undergoing minor and urological procedures is obviously low, hence mortality prediction in these groups has yet to be validated. However, because the morbidity predictive ability for these groups requires no additional weighting, it is probable that mortality is also adequately predicted. Thus, for the most part, the scoring system appears to cover the range of general surgical procedures, both elective and emergency, and allows prediction of both mortality and morbidity.

The use of increasing zones of mortality and morbidity rates, in particular the 10, 50 and 90 per cent prediction levels, can be useful when considering the expected mortality/morbidity risk for individual patients. It may be more important, and potentially more educational, to concentrate discussion of mortality and morbidity on patients falling below the 90 per cent line, rather than engaging in extensive discussion of those falling above the 90 per cent line. Equally profitable discussion could be extended to surgical success, for example the uncomplicated or surviving patient falling above an arbitrary line, say the 50 per cent line, where potential improvements in policy and management may be more apparent.

Obviously no regression equation for assessment of risk of morbidity and mortality should remain static over time; hopefully improvements in surgical management will occur. Logistic regression analysis of the observed mortality and morbidity rates on a hospital, district or regional basis would allow the 10–90 per cent ranges to be updated at regular intervals. The extrapolated score values (both physiological and operative severity scores) of 50 per cent risk of mortality and morbidity may potentially allow comparison between units or hospitals. Indeed comparison of physiological and operative severity scores of patients undergoing similar procedures in different units may be of benefit by highlighting different operative and management practices, and also differing modes of presentation.

Although POSSUM may not be able to replace highly specific scoring systems for individual disease states or the intensive care patient it does appear to provide an efficient indicator of the risk of morbidity and mortality in the general surgical patient. We should stress that our main intention is that POSSUM be used as an adjunct to surgical audit. It was never intended to affect the decision to operate, a decision that must always remain clinical. It could theoretically assist in the direction of resuscitative efforts.

The present study is our assessment of POSSUM at one hospital. We are at present assessing POSSUM in five different types of hospital across the Mersey Region In addition we are comparing POSSUM with a range of other scoring systems and examining the impact of physiological score manipulation, by preoperative resuscitative measures, on mortality and morbidity rates

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Case report

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Hepatocellular carcinoma complicating primary sclerosing cholangitis

T. Ismail, L. Angrisani, S. Hübscher* and P. McMaster

*The Liver Unit, Queen Elizabeth Hospital and *Department of Pathology, University of Birmingham, Birmingham, UK*

Correspondence to. Mr T. Ismail, Liver Research Laboratories, Queen Elizabeth Hospital, Birmingham B15 2TH, UK

Primary sclerosing cholangitis is a condition of unknown aetiology and ill-defined progression. Although a rare cause of chronic liver disease, it is the third most common indication for orthotopic liver transplantation[1]. The incidence of malignancy complicating primary sclerosing cholangitis is high[2]; nearly all tumours that occur with the condition are cholangiocellular carcinomas. The association of hepatocellular carcinoma occurring in a patient with chronic liver disease secondary to primary sclerosing cholangitis has not previously been well documented.

We describe a case of well differentiated hepatocellular carcinoma arising in a cirrhotic liver associated with primary sclerosing cholangitis.

Case report

A 39-year-old male Caucasian cabinet-maker presented in 1972 with pruritus and progressive jaundice. There was no history of alcohol abuse, blood transfusion or previous jaundice. At subsequent laparotomy, an operative cholangiogram was consistent with primary sclerosing cholangitis. Cholecystectomy and sphincterotomy were performed to improve biliary drainage. The patient then remained well until 1981 when he retired from his work because of increasing tiredness, fatigue and intermittent diarrhoea. Biopsies at colonoscopy confirmed ulcerative colitis throughout the colon. He settled on treatment with steroids and Salazopyrin® (Pharmacia, Milton Keynes, UK).

His general health gradually deteriorated and endoscopic retrograde cholangiopancreatography in 1984 confirmed changes consistent with primary sclerosing cholangitis with a major stricture at the hilum. This was initially managed by nasobiliary intubation and saline lavage without success.

In 1987, the patient presented with hepatosplenomegaly, gross ascites and variceal bleeding. This precipitated encephalopathy and he was referred to our unit for further assessment. On admission, he was thin, wasted, and had a soft irregular enlarged liver Investigations included serum bilirubin (47 µmol/l; normal range 5–20 µmol/l); alkaline phosphatase (1260 units/l, normal range 70–290 units/l); aspartate transaminase (91 units/l; normal range 5–20 units/l); haemoglobin (12·5 g/dl); prothrombin time (17/16 s); α-fetoprotein (58 kilounits/l; normal range <5 kilounits/l). Hepatitis B surface antigen and autoantibodies were negative and an isotope liver scan showed general reduction of uptake but no focal lesion. Percutaneous needle liver biopsy showed fibrous expansion of portal tracts with a lymphoid infiltrate and concentric fibrosis around medium-sized bile ducts After evaluation, the patient was accepted for the liver transplant programme

At transplantation in October 1987, a cirrhotic liver with gross portal hypertension and massive gastric varices were found. Total hepatectomy and liver replacement with a gallbladder conduit to a Roux-en-Y small bowel loop were performed. After operation the patient developed cardiorespiratory failure and septicaemia, and he died 17 days after transplantation. Gross examination revealed a green cirrhotic liver weighing 1060 g. On slicing, there were several discrete, pale brown nodules, the largest measuring 4 cm in diameter. Histological examination confirmed the presence of established cirrhosis with a mixed pattern of nodularity. There were occasional fibro-obliterative duct lesions and cystic dilations of intrahepatic bile ducts consistent with primary sclerosing cholangitis. The nodules seen macroscopically showed neoplastic transformation in the form of a well differentiated hepatocellular carcinoma with permeation of small vascular channels in surrounding fibrous septa. In addition, there was widespread liver cell dysplasia. Excision was complete with tumour negative nodes in the porta hepatis.

Discussion

As far as we are aware, this is the first case of classical hepatocellular carcinoma occurring in a cirrhotic liver complicating primary sclerosing cholangitis. The fibrolamellar variant of hepatocellular carcinoma associated with ulcerative colitis and primary sclerosing cholangitis has recently been reported[3]. The fibrolamellar variant of hepatoma generally occurs in young adults with non-cirrhotic livers and is said to have a relatively favourable prognosis[4]. One other case of hepatocellular carcinoma in a 26-year-old patient with primary sclerosing cholangitis has been reported[5]. Although no comment was made on the histological type, it may also have been a fibrolamellar variant as the liver parenchyma was non-cirrhotic with normal carcinoembryonic antigen and α-fetoprotein levels. The authors made particular reference to tumour recurrence in the graft following retransplantation for chronic rejection rather than the uniqueness of this occurrence. Combined hepatocellular and cholangiocellular carcinoma was found in one of eight patients with hepatobiliary tumours associated with primary sclerosing cholangitis and ulcerative colitis in a Mayo series[2].

The finding of hepatocellular carcinoma complicating primary sclerosing cholangitis has potentially important implications in the management of the condition. Management by means of reconstructive surgery or endoscopic manipulation is controversial. For end-stage liver disease due to primary sclerosing cholangitis, liver transplantation is now an accepted treatment option. Although cholangiocellular carcinoma is well recognized to occur in association with the condition, there appears to be a risk of hepatocellular carcinoma developing. Investigations should therefore include abdominal computed tomography and estimation of serum tumour markers (α-fetoprotein, neurotensin and vitamin B_{12} binding protein levels) in addition to routine screening. Intraoperative ultrasonography should be employed routinely at the time of hepatobiliary surgery.

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Hepatocellular carcinoma associated with primary sclerosing cholangitis and cirrhosis limits the role of potentially curative liver transplantation because of the risk of tumour recurrence. However, incidental primary liver tumours have a relatively good outcome[6]. This case report is the first to associate hepatocellular carcinoma with primary sclerosing cholangitis and cirrhosis, and highlights the importance of routine screening before and during operation for a parenchymal tumour mass.

Acknowledgements

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Surgical workshop

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Use of a resorbable mesh graft to obtain haemostasis from the cut surface of the liver after hepatic resection

R. Prêtre, G. Mentha and A. Rohner

Department of Surgery, Clinic of Digestive Surgery, Hôpital Cantonal Universitaire, Geneva, Switzerland

Correspondence to: Professor A. Rohner, Département de Chirurgie, Clinique de Chirurgie Digestive, Hôpital Cantonal Universitaire, 1211-Geneva 4, Switzerland

Haemostasis following hepatic resection may be difficult to achieve. Individual bleeding points are best treated by selective ligation or by sutures carefully placed in the parenchyma, while residual oozing is usually controlled by electrocautery and local tamponade. Various topical haemostatic agents are also frequently applied. It is customary then to cover the raw surface of the liver to maintain a tamponading effect, to minimize any leakage of bile and, perhaps, also to prevent subsequent visceral adhesions. The omentum and the falciform ligament have long been recognized as the best materials for this purpose[1]. The omentum in particular serves as both a source of tissue thromboplastin to promote local coagulation and as a large source of macrophages and lymphatic vessels to carry away dead cells and tissue debris. However, the omentum is not always available, while the falciform ligament is frequently too short or has already been destroyed. Construction of another autologous flap from Gerota's fascia has been described[2]. Although it creates a communication between the abdominal cavity and the retroperitoneum, no related complications have been reported. In circumstances when an autologous flap was not readily available, we have employed a resorbable mesh graft of polyglycolic acid, anchored at the hepatic capsule, to achieve haemostasis of the liver surface (*Figure 1*). Results of this technique are briefly reported.

Patients and methods

The data were derived from a review of the records of 153 patients undergoing hepatic resection (1983–89) in the Clinic of Digestive Surgery at Geneva University Hospital. In this series, 13 patients (8 per cent) had persistent bleeding of the cut surface of the liver despite selective suturing of bleeding points. These 13 patients received a mesh graft of polyglycolic acid to cover the cut surface of the liver and are the subject of this report.

There were seven right and three left hepatectomies, two right bisegmentectomies (one in a cirrhotic patient and one in a transplanted liver) and one right lobectomy (Couinaud's classification). The

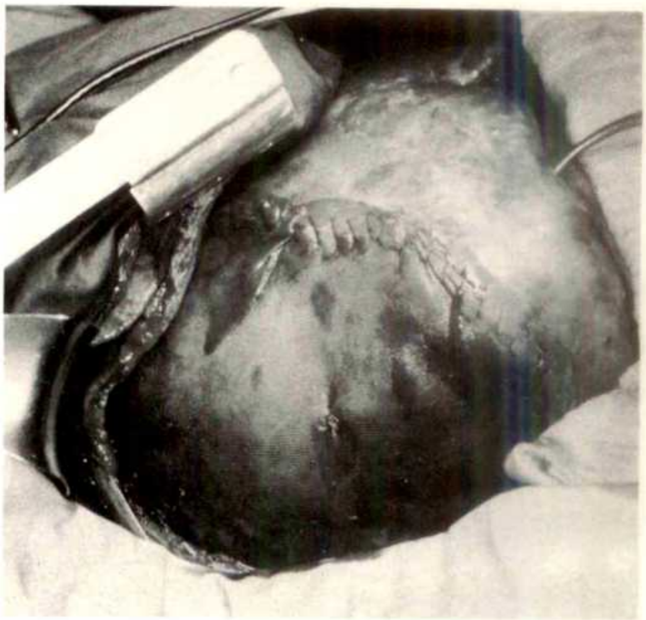

Figure 1 *Resorbable mesh graft sutured on to the resected margin of the liver. This 30-year-old patient had undergone urgent orthotopic liver transplantation for acute hepatic failure. He was reoperated on on the 23rd day after surgery for resection of infected necrosis of segments VI and VII. Haemostasis had been difficult to obtain and the mesh was applied to help eliminate residual oozing. Bleeding stopped as assessed both clinically and by a 'second look' on the following day. Sepsis did not persist even with immunosuppressive therapy. The patient was discharged home soon afterwards, and is currently well*

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resections were the only procedures performed in all cases and were electively undertaken in 12 patients. In the remaining patient, the resection was carried out to eradicate an infective focus. All patients had persistent bleeding from the hepatic margin in spite of normal or corrected coagulation factors. The Vicryl® (Ethicon, Johnson and Johnson SA, Spreitenbach, Switzerland) mesh employed measured 25 × 15 cm. The mesh has elastic properties in one direction that can be used to obtain a constrictive effect on the liver margin. The mesh graft was circumferentially anchored to the hepatic capsule (*Figure 1*). Posteriorly, it was in some cases sutured to the fibrotic sheath surrounding the inferior vena cava. Microcrystalline collagen powder was frequently packed between the hepatic surface and the mesh graft. All patients received perioperative antibiotic coverage. All abdomens were drained at the end of the procedure.

Results

There were no deaths after operation (death within 2 months or before hospital discharge). Four patients received up to two units of packed red cells in the first few days after operation; in no case was an active abdominal bleed suspected. Five patients displayed a transient low grade fever, but without clinical evidence of intra-abdominal infection or abscess. One patient underwent percutaneous drainage on the eighth day after surgery for a collection of serous fluid at the resection site. Computed tomography revealed that the mesh graft was well applied to the resection surface of the liver. Cultures remained sterile and no further treatment was required. This was the only significant postoperative complication encountered in this small group of patients.

Discussion

Application of a resorbable mesh graft to tamponade oozing from a transected parenchymal surface is employed in trauma patients after control of local bleeding points has been established. It has been used most frequently to achieve haemostasis of a disrupted spleen[3]. In our experience, in the context of liver surgery, the mesh is easy to apply and no more than a few minutes are required to suture it in place. Due to the circumferential fixation and the elastic properties of the mesh, a mild constrictive effect upon the transection plane of the liver can usually be obtained. This, combined with the tamponading effect of the mesh, will stop residual oozing of blood. We consider that implantation of mesh grafts to the liver margin is an effective and safe technique to help control bleeding when omentum or the falciform ligament are not available.

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The Vascular Surgical Society of Great Britain and Ireland

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The following abstracts are from the papers presented at a tripartite meeting of the Vascular Surgical Societies of Great Britain and Ireland, Canada and Holland, held at Kensington Town Hall, London, UK, 22–23 November 1990

Laser-assisted balloon angioplasty: a critical review

D.A. Ratliff, P.D. Fry, D.L. Doyle and Y. Hsiang, *University Hospital, Vancouver, Canada*

Following Cumberland and Sanborn's report in 1986, there has been a great deal of interest in the ability of lasers to recanalize occluded peripheral arteries. Whilst Dietrich continues to describe excellent results, Perler and White recently found a cumulative patency of 29 per cent at 1 year for successfully lased femoropopliteal occlusions and cautioned against excessive enthusiasm for laser angioplasty

Since June 1987 we have performed thermal angioplasties in 54 occluded femoropopliteal segments. A Trimedyne argon laser probe was used in 49, a NdYAG sapphire tip in one and a radiofrequency thermal probe in five Indications were more than half block claudication in 39 limbs (74 per cent), less than half block claudication in 5 (9 per cent) and limb salvage in 9 (17 per cent). Initial success was achieved in 34 (63 per cent) limbs. Cumulative patency figures for successfully lased vessels and all vessels treated are as follows· 76 and 48 per cent respectively at 1 month, 61 and 35 per cent at 6 months, 46 and 24 per cent at 1 year, 35 and 15 per cent at 2 years, and 22 and 7 per cent at 30 months. There was no case of limb loss attributable to laser use Primary failure was due to perforation in 17 of 20 limbs All sealed off

After the initial flurry of activity and enthusiasm, the role of laser-assisted balloon angioplasty is currently being re-evaluated and we believe that these results reflect the majority experience with this technique. Although further advances are needed, the laser in its present form is undoubtedly successful in some patients and more work is required to identify this group

Use of intraoperative streptokinase as an adjunct to balloon embolectomy

K.A. Harris, C. Barnes, E. Carroll, G. DeRose, W. Jamieson, E. Meads, J. Sweeney and R. Kozak, *St. Joseph's and Victoria Hospitals, London, Canada*

Propagation of clot distal to an embolus may render the balloon embolectomy catheter ineffective in removing the thrombus. Although percutaneous infusion of thrombolytic agents has been reported, it is complicated by bleeding and requires a prolonged length of time for clot lysis. We hypothesize that mechanical removal of clot within large vessels followed by thrombolysis of small vessel occlusions is a safe and effective method of improving limb salvage To mimic the clinical situation of small vessel thrombosis, 18 New Zealand white rabbits had thrombin generated autologous clot infused into each iliac artery One artery was then treated with streptokinase (SK) infused in one of three doses (A=2500 U; B=5000 U; C=10000 U) and the contralateral limb served as a control (C). Angiograms were obtained before and after infusion and ranked according to the degree of clotting (1=patent, 2=partially occluded, 3=occluded) in the iliac, femoral and tibial segments. The degree of generation was similar in both the SK and C groups. There was a significantly ($P<0{\cdot}05$) greater number of improved limbs in the SK group ($n=18$) when compared to the control limbs ($n=11$). The percentage of improved segments is as follows. Iliac: SK=95 per cent, C=97 per cent; femoral; SK=79 per cent, C=32 per cent, tibial: SK=42 per cent, C=5 per cent All dose groups showed a significant improvement with the thrombolytic infusion although the effect remained more marked in the distal arterial segment. Although there was a decrease in fibrinogen levels (pre-infusion $2{\cdot}29 \pm 0{\cdot}50$, postinfusion $1{\cdot}77 \pm 0\ 70$), these did not result in clinical bleeding. It was concluded that the intraoperative infusion of streptokinse may be a safe and efficacious method of removing clot from vessels inaccessible to a balloon catheter

Thrombolysis with tissue plasminogen activator and streptokinase in occluded arterial grafts

H. Stigter, *St Radboudziekenhuis, Nijmegen, The Netherlands*

The efficacy of tissue plasminogen activator and streptokinase was evaluated in thrombosed prosthetic grafts, aged *in vivo* for 1, 6 or 48 h, in the carotid artery of beagle dogs Graft patency was confirmed with interval angiography and electromagnetic flow measurements

Either local streptokinase (100 U kg^{-1}) or systemic or local tissue plasminogen activator (30000 U kg^{-1}) plus heparin (17·5 U kg^{-1} with a loading dose of 25 U kg^{-1}) was administered during 1 h. α_2-Antiplasmin and fibrinogen levels were measured in frozen blood samples taken before and during thrombolytic therapy

Numbers for reperfusion of occluded grafts of different age in different treatment groups were as follows

			Recombinant tissue plasminogen activator	
Age (h)	*n*	Streptokinase	Local	Systemic
1	14	3/4	1/4	5/6
6	12	1/4	0/4	2/4
48	15	0/6	0/5	0/4

In all three treatment groups a minimal decrease in fibrinogen levels (to about 85 per cent of pre-infusion values) was observed With tissue plasminogen activator infusion α_2-antiplasmin levels dropped to 58 per cent of pre-infusion values

In our model, tissue plasminogen activator and streptokinase seem moderately but equally effective in lysing occluded grafts, while older thrombi are progessively more difficult to lyse It is unclear whether a decrease in α_2-antiplasmin level during tissue plasminogen activator infusion reflects a systemic fibrinolysis.

Groin haemorrhage complicating intra-arterial thrombolytic therapy: choice of technique and agent

K. Dawson, E Dex, A. Platts and G. Hamilton, *Royal Free Hospital, London, UK*

Intra-arterial thrombolysis is effective in the treatment of acute peripheral vascular ischaemia with streptokinase (SK), urokinase and, more recently, tissue plasminogen activator (r-TPA) being the most widely used agents Fear of haemorrhagic complications has perhaps limited more widespread use in the UK The most common of these complications is groin haemorrhage around the arterial catheter, reported in 10–30 per cent of cases. We report our evolving experience to date with reference to changes of thrombolytic agent and infusion technique with a subsequent improvement in the incidence of groin haemorrhage Thirty-seven patients were treated by thrombolysis for acute lower limb ischaemia. The major amputation rate was 6·25 per cent and mortality was 18·7 per cent at 30 days The first 18 patients were treated with a low dose of SK (5000 U h^{-1}) The next 19 patients were treated with r-TPA (0 5 mg h^{-1}) and in these the arterial catheter sheath was left *in situ* in the vessel in an attempt to control bleeding around the catheter from the arterial puncture site. The sheath side port was also infused with r-TPA to prevent pericatheter thrombus All angiograms were performed by a radiologist in the X-ray department. There was no statistical difference in age or ischaemic time between the two treatment groups, although the infusion time required for successful lysis was less with r-TPA ($P=0\ 01$). There were 6

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haemorrhages in the 18 SK-treated patients (33 per cent), with 2 requiring transfusions. The r-TPA group had 1 haemorrhage in 19 patients (5·3 per cent), with no transfusions These results are significant (χ^2 P=0·03). The thrombus-specific agent r-TPA has improved efficacy in our experience and we have now shown that its use in combination with a retained arterial catheter sheath can significantly reduce the incidence of groin haemorrhage to an acceptable clinical level

A simple *in vitro* test to estimate heparin dose

S. Leavey, M. Murphy, N. Williams, R. O'Donnell, P. Grace and D. Bouchier-Hayes, *Beaumont Hospital, Dublin, Ireland*

There is a wide variability in anticoagulant response to a standard dose of heparin. Consistent adequate anticoagulation requires the calculation of an individual heparin bolus, but doses estimated on body weight are not accurate We, therefore, developed a method of calculating *in vitro* the heparin dose required to achieve anticoagulation in a given patient.

Fifteen patients were studied Blood samples were diluted with five concentrations of heparin (0, 0·2, 0·4, 0·6, 0·8 U m^{-1} plasma) The APTT of each sample was measured and plotted against heparin concentration (r=0·974–1·000). The concentration of heparin at 2·5 times normal APTT was estimated from the graph and multiplied by the plasma volume (from body dimensions) to give the required heparin bolus. APTT was measured 10 min after bolus injection. The following results were obtained.

The median *in vitro* heparin concentration per ml of plasma required to achieve 2·5 times APTT was 0·47 U ml^{-1} (0·40–0·75). The median heparin bolus given was 1490 U (1044–2000 U). The median percentage of predicted APPT achieved was 73 per cent (56–123 per cent) All 15 patients were adequately anticoagulated with the predicted heparin bolus.

The simple *in vitro* technique described can be used to individualize the dose of heparin required to achieve adequate anticoagulation. We suggest that this test will eliminate the excessive anticoagulation produced by blind bolus administration of heparin.

Angiographic assessment of arterial outflow in patients undergoing aortobifemoral bypass reconstructions: the predictive value of a new classification system

M. Stein, F. M. Ameli, R. Gray, H. Grosman and L Aro, *The Departments of Vascular Surgery and Radiology, The Wellesley Hospital, Toronto, Canada*

The purpose of this study was to use a numerical reproducible system for the classification of arterial outflow and to predict the outcome of aortobifemoral bypass surgery using the above system. We report a prospective study with 4 years of follow-up involving 127 consecutive symptomatic patients (60·0 per cent), claudication, 39·4 per cent critical ischaemia) undergoing aortobifemoral bypass surgery. Preoperative angiograms were numerically assessed according to the arterial outflow status at the level of main segmental involvement, both femoral, profunda and run-off at the popliteal level. The criteria for scoring were (A) the relative importance of the outflow artery and (B) the degree of occlusion. The higher the score, the worse the outflow.

Angiography scores ranged between 1 and 10 with a mean of 3·6±0·24. The main comparison was between patients with scores of <5 (group A, n=80) and patients with scores of 5 or more (group B, n=47). Better outflow was associated with higher postoperative mean increases in the ankle/brachial index (ABI) (A=0·35±0·03, B=0·17±0·04, P<0·001) and transcutaneous oximetry (P_{tc,O_2}) (A=15·4±1·8 mmHg, B=8·4±3·0 mmHg, P=0·01). At four years of follow-up, group A had higher cumulative rates of patency (A=98·3 per cent, B=78·0 per cent, P<0·001), symptomatic relief (A=84 per cent, C=23·3 per cent, P<0·001) and palliation (A=67 per cent, B=19·9 per cent, P<0·001).

In conclusion, angiographic outflow, as evaluated by our system, successfully predicted postoperative increases in ABI and P_{tc,O_2} and the cumulative rates of graft patency, symptomatic relief and palliation. Its prognostic value makes it an important factor in the pre-operative assesment of patients undergoing peripheral vascular surgery.

Assessment of computerized tomography scans in aortic aneurysms

J A. Carlson and D.L. Wooster, *St. Joseph's Health Centre, University of Toronto, Toronto, Canada*

Compterized tomography (CT) is used to assess size of abdominal aortic aneurysm (AAA) and its relationship to the renal and iliac arteries and retroperitoneal structures. To gain more information from CT, descriptors were identified to quantify the diameter and length of AAA and its wall and thrombus characteristics The descriptors were applied to CT results in 35 patients. The measurements were reproducible within each study and correlated with operative findings except for iliac artery involvement (15 per cent false negative) Diameter correlated with length of AAA. Renal (7 per cent) and iliac (37 per cent) artery involvement correlated with length ≥10 cm but not with diameter. Degree, location, arc or pattern or mural calcification did not relate to length or diameter. Thrombus area showed a linear relationship to sac area (r=0·95). no difference in thrombus location or thrombus/lumen ratio was identified except in three cases (8 per cent) which may represent unstable AAA. Disruption of thrombus and frank leakage was seen in too few cases to generalize. Wall thinning to ≤1 mm was found in six with no relationship to other factors. Analysis of risk factors showed non-smokers to have larger aneurysms (8·0 versus 6·1 cm) and normotensive patients had more dorsal located thrombus. No difference was found with sex, age or coronary artery disease.

This study provides a basis for better understanding of wall characteristics of AAA and may identify potential for rupture. With the development of detailed protocol for CT in AAA such data may be helpful in timing operations. A multicentre study of large numbers of CT scans is suggested.

Ruptured abdominal aortic aneurysm: 30 years experience

C. Iannicello, A.R. Downs, J. Farr, C. Lye, H. Fong and A. Katz, *Department of Surgery, University of Manitoba, Winnipeg, Manitoba, Canada*

A retrospective review of 267 ruptured infrarenal abdominal aortic aneurysms operated upon between 1958 and 1987 was performed. All data was documented and computerized A univariate analysis was performed for eight variables using χ^2 analysis. Stratified analysis was performed for survival related to pre-operative shock and blood replacement. The mean age was 72 years and, except for the first 6 years, there was no change in the average age of operated patients. There were 226 males and 41 females with the ratio of 6 to 1. Pre-operative shock was present in 210 patients. A previous history of hypertension was obtained in 98 patients. Overall operative mortality was 41 per cent Thirty-two deaths occurred in the operating theatre The duration of rupture prior to operation did not affect survival. Aneurysms <5 cm in diameter had a significantly lower mortality and those greater than 10 cm had a significantly higher mortality than those between 5 and 10 cm. Peri-operative shock, oliguria, blood replacement and patient's age were the factors most affecting survival Shock and myocardial infarction accounted for 75 per cent of the deaths With the exception of the first 6 years of the study period, there has been no significant change in the operative mortality rate. Patients >80 years of age with a prior history of cardiac disease and pre-operative shock had a mortality rate approaching 90 per cent Over the study period, 90 per cent of the operations were performed by four surgeons. The survival curve of those patients discharged from hospital is parallel to that for a comparable age group.

Classification of ruptured abdominal aortic aneurysms

M. Callam, D. Haiart, J. Murie, C. Ruckley and A. Jenkins, *Royal Infirmary, Edinburgh, UK*

The interpretation of the results of operation for ruptured aortic aneurysm has recently been a matter of debate. Controversy relates to the number and nature of the exclusions from published studies. Different referral and selection practices give different results. A comprehensive classification for ruptured aneurysm would be useful The alpha-numeric categories proposed deal with all possibilities from undiagnosed aneurysmal death in the community to survival more than 30 days after operation.

The classification has been applied prospectively to 100 consecutive patients referred to the regional vascular service (from January 1989 to April 1990) Categories A–C2 cover ruptures not referred and are not included.

Class	Description	Number
C3/D	Patients dying at peripheral hospital/in transit	2
E	Patients dying in Accident and Emergency before decision taken	4
F1	Patients considered unsuitable for surgery	19
F2	Patients refused surgery	1
G1–4	Patients dying en route to or in theatre	9
H/S	Patients surviving theatre	65
C3–S	All referred patients	100

The above figures may be used to demonstrate an 'operative' mortality rate of 17–50 per cent, depending on how they are used. The proposed classification offers the possibility of a much needed standardization in the reporting of treatment of ruptured aneurysm as the degree of case selection can be quoted, e.g. groups C3–S in the above example.

Abdominal aortic aneurysms in 4237 screened patients from a general practice population: prevalence development and management over 6 years

R.A.P. Scott, H.A. Ashton and D.N. Kay, *St. Richard's Hospital, Chichester, West Sussex, UK*

Ruptured abdominal aortic aneurysm (AAA) in our registration districts accounted for 1·2 per cent of all deaths in one year and of these 61 per cent died outside hospital. Identification and treatment of the disease before rupture through screening and careful management of patient groups most at risk has the potential to reduce this mortality An ultrasound screening programme was set up and made available to 7200 unselected patients aged between 65 and 80 from family practitioner lists A total of 4237 have been screened over 6 years (an acceptance rate of 58·8 per cent) and the aorta was identified successfully in 97·3 per cent of patients.

Aortic dilatation of 3 cm or greater was found in 179 patients. 148 men (7·6 per cent) and 31 women (1·4 per cent) Repeated scans over a follow-up period of up to 6 years have shown that the aneurysms increased in size in 39 per cent of patients. Criteria for considering surgery have been developed based on aneurysm size, expansion rate and symptom development. Only 16 aortic aneurysm repair operations have been performed on this group (8·9 per cent of those with detected aneurysms), and yet no patient has died from ruptured AAA Surgery is not inevitable for all patients found to have an AAA, and by following guidelines for management, screening offers benefits to the patient and health service and does not appear to lead to an excessive workload for the vascular surgeon.

Follow-up of small aortic aneurysms in patients over 75 years of age

B. Lether and K.F.W. Smink, *Haarlem, Spaarne Ziekenhuis, The Netherlands*

Sixty-one patients aged 75–91 years had an abdominal aortic aneurysm 3·0–4·5 cm in diameter diagnosed from 1980 through 1986. These patients were followed-up prospectively every 3–6 months by serial echoscans. Follow-up was for at least three years or until death The cause of death was confirmed by autopsy in 77 per cent of patients who died before January 1990. Four patients (7 per cent) had ruptures during follow-up Three of these four patients died Two aneurysms (3 per cent) were <5 cm in diameter at the time of rupture. During follow-up, the aneurysm reached 5 cm or more in greatest diameter in 19 patients (31 per cent). Eleven patients underwent elective repair of their abdominal aortic aneurysm One patient (9 per cent) died postoperatively

In eight patients it was decided not to operate Two of these eight patients (25 per cent) died because of rupture of their aortic aneurysm. Our data suggests that follow-up of small aortic aneurysms (3·0–4·5 cm) in patients over 75 years of age is a relatively safe approach until the aneursym reaches 5 cm in greatest diameter.

Optimum rescreening interval for abdominal aortic aneurysm

B. Heather, J. Collin and J. Walton, *John Radcliffe Hospital, Headington, Oxford, UK*

The prevalence of abdominal aortic aneurysm in men aged 65–74 years is 5·5 per cent but incidence screening has never been performed and the optimal rescreening interval is unknown Analysis of the data on growth rates of small AAAs should allow recommendations to be made for the frequency of review ultrasound examinations for preclinical AAA detected by screening and for optimal incidence screening (rescreening) intervals for the population at risk

One hundred patients with AAA of 2·5–3·9 cm in diameter were re-examined by ultrasound every 6 months for up to 3 years after diagnosis The annual growth rate was calculated for each aneurysm until its diameter exceeded 3·9 cm after which further data was excluded from analysis

The initial aneurysm diameters were: median 2·9 cm, range 2·5 to 3·9 cm, and mean ±s.e. 3·03±0·04 cm. In 15 patients the AAA grew to 4·0 cm or more and 5 of these with aneurysms of 4·2 to 5·7 cm diameter have undergone elective aneurysm surgery The annual incremental growth rates were median 0·1 cm, range −0·4 to 1·6, and mean ±s.e. 0·19±0·04 cm. The increase in diameter was >0·5 cm per annum in 12 patients and ⩽0·2 cm per annum in 69 patients.

We conclude that for aneurysms <4 cm in diameter, 6 months remeasurement is enough. In a population at risk for AAA, rescreening at intervals of <5 years is unlikely to be worthwhile

Treatment policy in asymptomatic abdominal aneurysms: a Markov decision analysis

P.J.E.H.M. Kitslaar and J. Kievit, *University Hospital Maastricht and University Hospital Leiden, The Netherlands*

In patients with asymptomatic abdominal aortic aneurysm (AAA) >3 cm diameter, three treatment policies are possible. (1) Prophylactic operation soon after discovery, irrespective of AAA size. (2) Regular echo monitoring, followed by elective operation at a certan diameter of the AAA (3)Expectant, operating only for symptoms or rupture.

The strategy which would result in the longest remaining life-expectancy (=utility), was determined in a computerized Markov analysis (software Decision Maker 6·0), simulating the outcome of each policy (death or one of eleven possible states of health) in cycles of one year The variable values used in this analysis were: natural mortality for age, AAA growth rate (52 mm/year), AAA rupture risk, (0·8–9·3 per cent/year, depending on size), pre-hospital mortality of AAA rupture (38 per cent), operation mortality (elective 6 per cent, rupture 45 per cent), risk of prosthesis infection (0·8 per cent/year), an anastomotic aneurysm (0·4 per cent/year), mortality of secondary operations (anastomotic aneurysm 6 per cent), prosthesis infection 30 per cent). Operation mortalities were adjusted for patient age and American Society of Anaesthesiology (ASA) score

Based on the Markov analsis and a three-way sensitivity analysis for age, ASA status of the patient and diameter of the AAA, simple diagrams could be constructed showing the policy with the highest utility for an individual patient These diagrams might be customized for the individual surgeons by the use of own variable values in the Markov analysis.

Diagnosis of inflammatory aneurysms of the abdominal aorta: serological and radiological investigation

W.G. Tennant, M.G. Wyatt, G. Hartnell, R.N. Baird and M. Horrocks, *Vascular Studies Unit, Bristol Royal Infirmary, Bristol, UK*

Inflammatory aneurysms of the abdominal aorta comprise 10–15 per cent of all aortic aneurysms. Reliable pre-operative diagnosis is important, as repair may require considerable modification of surgical technique to reduce morbidity and mortality.

We report our initial findings on the use of serological markers in the diagnosis of inflammatory aneurysms, and our investigation into the use of magnetic resonance imaging (MRI), computerized tomography (CT) and ultrasound in aneurysm patients. Four groups of patients were studied prospectively.

1. Inflammatory aneurysms ($n=11$)
2. Non-inflammatory aneurysms ($n=61$)
3. Aorto-iliac occlusive disease ($n=35$)
4. Age matched control patients ($n=14$)

Plasma viscosity, elastase-antitrypsin complex, α_1-antitrypsin, C-reactive protein and caeruloplasmin were assayed in fasting blood samples taken from all patients pre-operatively The diagnosis of inflammatory aneurysm was made at operation in all cases, and confirmed histologically. All five serological markers were raised in patients with inflammatory aneurysms compared to all other patient groups ($P<0·05$ in all cases, Mann–Whitney) The diagnosis of inflammatory aneurysm was made pre-operatively in all cases using MRI. This investigation was twice as sensitive as CT in making the diagnosis of inflammatory aneurysm. Ultrasound was unhelpful in all cases.

The presence of raised levels of one or more of the serological markers in aneurysm patients may act as a useful clinical guide to the presence of inflammatory aneurysm. MRI is the most useful test for diagnostic confirmation and accurate assessment of extent.

Impact of cardiac nuclear ventriculography on planning for elective aortic surgery

P. Foex, P.J. Clarke, O. Omerod, P. Lamont, J. Collin, D. Gray and P.J. Morris, *John Radcliffe Hospital, Oxford, UK*

Surgery for patients with vascular disease is inevitably associated with morbidity and mortality related to the cardiovascular system. In an attempt to minimize this risk, 34 patients with aorto-iliac occlusive disease and 41 with aneurysmal disease underwent pre-operative cardiac assessment with electrocardiograph (ECG), chest radiograph and multiple gated cardiac scintigraphy with exercise or Persantin-induced stress (MUGA scanning)

Clinical examination plus the pre-operative ECG were found to be unreliable discriminators when used to detect patients with poor left ventricular function: specific ECG evidence of a previous myocardial infarction (MI) correlated poorly with resting cardiac ejection fractions, which ranged from 25–72 per cent under these circumstances Patients with a resting ejection fraction of under 30 per cent were considered to pose an unacceptable operative cardiac risk. Using this criterion, only 27 patients (79 per cent) with occlusive disease and 29 patients (71 per cent) with aneurysmal disease underwent surgery as planned. The management of the remaining 17 out of 75 patients was altered as follows. Three patients had surgery postponed in order to improve cardiac status Four patients with occlusive disease underwent a less extensive surgical procedure than that initially planned. Ten patients were cancelled because the risk of surgery was thought to be unjustified. Of these, seven had asymptomatic aneurysms who are currently being followed by ultrasound.

Post-operative cardiovascular morbidity occurred in two patients in the occlusive group (one MI and one mild cardiac failure), and in four patients in the aneurysm group (three with atrial fibrillation and one MI). Three patients died postoperatively and one of these deaths was due to an MI.

In conclusion, pre-operative cardiac assessment with MUGA scanning altered patient management in a total of 17 patients (23 per cent). Of those patients who underwent surgery, cardiac morbidity was low (8 per cent), and there was only a single cardiac death This investigation is a valuable adjunct to pre-operative cardiac assessment in patients before aortic surgery.

Intravascular high frequency imging of small vessel morphology

H. Van Urk, W.J. Gussenhoven, G.P. Gerritsen and N. Bom, *Department of Surgery, University Hospital, Rotterdam, The Netherlands*

Percutaneous transluminal recanalization techniques have become generally accepted as an alternative or adjunct to vascular surgery in the treatment of peripheral atherosclerotic stenotic and/or occlusive disease. Differences in morphologic structure of stenosed and/or totally occluded vessel wall limit the various recanalization procedures, such as balloon-angioplasty, laser-angioplasty and the atherectomy (Simpson) catheter The inability to differentiate between atherosclerotic plaque and vessel wall may lead to accidental perforation of the vessels. Direct angioscopy is of limited use for complete occlusions and cannot identify calcification in a plaque.

In order to assess the morphology and dynamic wall motion of small vessels both before and after recanalization, we developed a catheter tip high frequency ultrasonic imaging device for intravascular application. A single element (40 MHz) transducer was mounted on a 2 mm catheter The system provides a 360° image of the vessel interrogated, with real-time images of 50/s.

A series of *in vitro* studies on normal and diseased arteries accurately demonstrated internal lumen geometry and vessel wall issue characteristics. The real-time images correlated extremely well with the histopathologic appearances Atherosclerotic lesions are recognized by their increased echogenicity. Subsequent *in vivo* studies in pigs have demonstrated further excellent clinicopathological correlations of both wall structure and dynamics. These studies are presented.

It is anticipated that the development of such a catheter tip imaging system combined with a recanalization method will be of immense benefit in the precise localization and identification of vessel wall pathology, the precise positioning and subsequent use of the recanalization procedure and in assessing the effect of recanalization.

Deep brachial and superficial femoral vein as auxiliary harvest sites for bypass grafting

J.G. Sladen, M.O. Riggs, J.D.S. Reid and T.M. Maxwell, *St Paul's Hospital, University of British Columbia, Vancouver, Canada*

As reconstructive vascular surgery becomes commonplace, secondary and tertiary harvest sites for autogenous vein have become increasingly important. Poor results are associated with veins of borderline diameter. We have used the deep brachial and superficial femoral veins as alternative harvest sites with gratifying results. This series represents 40 consecutive cases using these conduits from January 1987 to April 1989. There were 27 males and 13 females ranging in age from 22 to 88 years All were secondary or tertiary reconstructions with the majority (25) performed for limb salvage. Other indications included graft infection, false aneurysm, arm ischaemia and claudication. The deep brachial vein was harvested and used alone or in combination in all cases, and the superficial femoral vein in six cases. Eleven grafts were used in the femoral crossover position, 22 as major infra-inguinal reconstructions and the remainder for ileo-profunda, arm or lesser infra-inguinal reconstructions (i.e. 'jump grafts'). The application, technical considerations, pitfalls and results to date are presented

Quantitative histological assessment of white cell distribution in skin of patients with venous disease

H.J. Scott, G.M McMullin, P.D. Coleridge Smith and J.H. Scurr, *Department of Surgery, The Middlesex Hospital, London, UK*

It has previously been suggested that white cells have a primary role in the pathogenesis of venous ulceration[1]. In order to quantify the extent of white cell invasion of the skin a histological study has been undertaken. Nineteen patients admitted for surgical treatment of varicose veins were studied In five patients there was no clinical evidence of skin changes. Fourteen patients had lipodermatosclerosis (LDS), eight of whom had previously suffered venous ulceration. The extent of venous abnormality was confirmed using colour duplex ultrasound imaging and photoplethysmography

Patients rested supine initially for 30 min after which a 3 mm punch biopsy of the supramalleolar skin was taken under local anaesthesia. Patients then sat for 30 min without moving, following which another biopsy was obtained in the same region. A total of 2880 serial histological sections were cut and examined to determine the number of white cells per unit area in the upper 0·5 mm of the skin. An observer blind to the identity of the sections undertook this work. Results are given as white cells/mm^2 skin section (interquartile range).

	No skin change	LDS	LDS/ulcer history
Resting (1 h)	6·2*‡ (4·9–7·0)	45* (26–178)	217†‡ (107–224)
Standing (1 h)	8·3 (4·1–7·5)	42 (25–196)	190 (95–235)

* $P=0·03$, † $P=0·008$, ‡ $P=0·004$ (Mann–Whitney)

There were 8–35 times as many white cells in the liposclerotic skin than normal. This did not increase following a period of raised venous pressure produced by standing.

1. Coleridge Smith PD, Thomas PRS, Scurr JH, Dormandy JD The aetiology of venous ulceration – a new hypothesis. *Br Med J* 1988, **296**: 1726–8.

False aneurysms in intravenous drug abusers

G.H. Welch, D.B. Reid, G. Ramsay and J.G. Pollock, *Royal Infirmary, Glasgow, UK*

Intravenous drug abuse is a major problem in inner city areas in the UK. An increase in arterial trauma has been associated with this practice, due to deliberate or inadvertant arterial injection.

Nine patients, two of whom were positive for human immunodeficiency virus (HIV) and three of whom were positive for hepatitis B surface antigen, presented with infected false aneurysms (eight femoral, one brachial). Two patients had significant limb ischaemia at presentation. The first six patients underwent ligation and reconstruction; five grafts became infected with secondary haemorrhage in three All five grafts have been removed with no limb loss, although two patients were later regrafted for disabling claudication.

In view of this early experience with infection, a subsequent three cases were treated by ligation alone. We would now recommend a policy of 'selective delayed revascularization' performing initial ligation and debridement alone. Only if the limb is non-viable should reconstruction be performed, and then preferably via an extra-anatomic route. In the majority of cases viability will be maintained despite ligation of the external iliac/femoral arteries.

Elevated plasminogen activator inhibitor activity and hyperinsulinaemia in obstructive arterial disease

D.C. Aronson, E.J.P. Brommer*, A. Raben, M. Frohlich and J.H. van Bockel, *University Hospital and *Gaubius Institute TNO, Leiden, The Netherlands*

High levels of plasminogen activator inhibitor (PAI) resulting in a low fibrinolytic activity of the blood have been described in patients with coronary artery disease. Enhanced PAI synthesis has been attributed to hyperinsulinism There is also evidence for decreased fibrinolytic activity in peripheral artery disease, but a study of PAI has not yet been published.

We investigated 48 patients (34 men, 14 women) who attended the outpatient clinic with early-onset obstructive arterial disease, diagnosed before the age of 45 years. Their mean(s.d.) age was 39·7(6·8) years at the time of investigation. None had manifest diabetes mellitus. As a control group we studied 48 patients (30 men, 18 women) with minor surgical problems, without apparent underlying disorders, mean age 30·4(7·3) years.

Mean(s.d) PAI activity was significantly higher in patients (221(180) per cent of normal reference values) than in controls (119(114) per cent); mean(s d.) tissue plasminogen activator (TPA) antigen was significantly higher in patients (12 4(5·3) ng ml^{-1}) than in controls (8·4 ± 5 1 ng ml^{-1}) PAI activity, circulating partly in complex with TPA, correlated positively with TPA antigen, both in patients ($r=0{\cdot}57$, $P<0\,001$) and in controls ($r=0{\cdot}61$, $P<0{\cdot}001$). Correlation with age was positive only on the patient group ($r=0\,29$, $P<0\,05$), or in both groups taken together ($r=0\,48$, $P<0{\cdot}01$) Although we did not measure free TPA, fibrinolytic activity will be low in the presence of elevated PAI levels, despite high TPA antigen levels. A positive correlation was found between plasma PAI levels, and insulin and C-peptide levels ($r=0{\cdot}42$, $P<0{\cdot}01$ and $r=0{\cdot}58$, $P<0{\cdot}001$, respectively).

PAI activity and TPA antigen are elevated in patients with early-onset obstructive arterial disease. A constantly low fibrinolytic activity might enhance arterial obstruction by fibrin deposits. The high PAI levels could be associated with hyperinsulinism

Surgical treatment of arteriosclerotic renovascular hypertension: effect on non-fatal cardiovascular events during follow-up

J.H. van Bockel, P.C. Chang, J. Hermans, J. Willemsen, A. Ludlage and J.L. Terpstra, *University Hospital, Leiden, The Netherlands*

Between 1959 and 1989, 132 hypertensive patients underwent renal artery reconstruction for arteriosclerotic renovascular disease. Preoperative data were collected on target organ damage (TOD) and extrarenal arteriosclerosis (ERA) present in 64 per cent of patients Postoperative data were obtained at short-term (mean 8 months) and long-term (mean 9 years, range: 1–24 years) intervals after surgery. At these intervals, the blood pressure response (BPR) to surgery and all non-fatal cardiovascular events (CVE) were recorded

Nine patients died within 1 year after the operation and two were lost to follow-up. At the short and long-term intervals, the BPR was beneficial (cured or improved) in 76 and 71 per cent of the patients, respectively. Both at the short and long-term intervals the BPR was not significantly influenced by the pre-operative presence or absence of TOD and ERA (beneficial BPR in 76 versus 71 per cent) Patient survival at 10 years was better with beneficial (80 per cent) than with failed (61 per cent) BPR at short-term ($P=0\,016$). A multivariate analysis of patient survival including age, pre-operative TOD and ERA, the short-term interval BPR and the short-term systolic and diastolic blood pressure, demonstrated that a systolic blood pressure ≥ 170 mmHg only was associated with reduced 10 year survival Analysis of the effect of operation on non-fatal CVE (angina, myocardial infarction, cardiac insufficiency, stroke and TIA) showed that a short-term beneficial BPR was associated with a reduction of 60 per cent in events per 100 months at risk This effect was especially conspicuous in the presence of ERA (72 per cent) but hardly noticeable in its absence (4 per cent).

Surgical treatment of renovascular hypertension may favourably influence blood pressure regulation, long-term survival and long-term cardiovascular morbidity independent of the pre-operative presence of TOD and ERA. A systolic blood pressure ≥ 170 mmHg at the short-term interval is the only predictive parameter for long-term patient survival.

Mannitol prevents neutrophil activation during aortic surgery

I.S. Paterson, A Hanbury, N. Browning, S. O'Dwyer, W. Wallbank and D. Charlesworth, *University Hospital of South Manchester, Manchester, UK*

The neutrophil oxidative burst which follows ischaemia and reperfusion is related to the prostaglandin derivative thromboxane. Oxygen free radicals from reperfused tissue initiate thromboxane production and subsequent white cell activation. Mannitol, a hydroxyl radical scavenger, is effective in limiting ischaemia-induced thromboxane synthesis during aortic aneurysmectomy

We investigated whether, during aortic surgery, ischaemia and reperfusion activate neutrophils and also the ability of mannitol to inhibit this process. Twelve patients undergoing elective aortic aneurysmectomy were randomized prospectively to receive 0·2 g kg^{-1} mannitol ($n=7$) or an equivalent volume of saline ($n=5$) as a short intravenous infusion prior to clamping. Blood was sampled before, during and after cross clamping for estimation of thromboxane (radio-immunoassay) and neutrophil oxygen free radical production (dichlorofluorescein oxidation). Neutrophils isolated from separate blood samples at each time point were treated with phorbol myristate acetate (PMA) 10–7M to assess responsiveness. In the saline treated group, plasma thromboxane levels increased from a pre-ischaemic value of 124 ± 24 pg ml^{-1} to 268 ± 64 pg ml^{-1} ($P<0{\cdot}01$) after 15 min ischaemia and to 397 ± 105 pg ml^{-1} after declamping ($P<0{\cdot}01$). Free radical production from neutrophils increased from a pre-ischaemic value of 17 ± 4 mean fluorescein units to 56 ± 6 after clamping and to 120 ± 12 after declamping (both $P<0\,01$) PMA treatment of isolated neutrophils produced an enhanced free radical response in reperfusion samples Mannitol pre-treatment prevented the increases in thromboxane levels, the increased neutrophil free radical production, and the enhanced oxidative response of reperfusion neutrophils to PMA.

In conclusion, mannitol prevents neutrophil activation during aortic surgery perhaps by preventing ischaemia-induced thromboxane synthesis

Detrimental effect of smoker's serum on cultured large vessel endothelial cells

R.S. Kiff, M.S.F Clarke, S. Kumar, D.C. West and D. Charlesworth*, *Christie Hospital and *University Hospital of South Manchester, Manchester, UK*

Vascular endothelial cell (EC) injury by cigarette smoking probably influences the pathogenesis of atherosclerosis The mechanism of damage, however, is not understood, although nicotine has been implicated. This study examined whether cigarette products and metabolites present in smokers' serum damage vascular ECs in culture

The effect of pooled serum from three groups of five smokers and similar pools from non-smokers ± nicotine was studied in adult human large vessel and umbilical vein and on fibroblast controls. Uniformly seeded cultures in 24-well plates were exposed in triplicate to various concentrations of serum in culture medium, replenished on alternate days. Proliferation was assessed daily on a Coulter counter and by DNA assay. Prostacyclin production was assessed separately over 24 h by radioimmunoassay for the stable metabolite in samples of the supernatant. Exposure of both EC types to smoker's serum, but not nicotine, induced a significant reduction in cell count and DNA synthesis ($P<0{\cdot}05$) by day 4 (20 per cent serum) and day 5 (5 per cent serum). Prostacyclin production was significantly less in smoker's serum ($P<0{\cdot}05$) Fibroblasts were not affected.

The results show that a constituent(s) of smoker's serum, other than nicotine, has a significant damaging effect on vascular endothelial cells from umbilical vein and from large vessel origin which has not previously been studied. This substance(s), a major cause of cigarette-related vascular disease, requires further evaluation.

Adverse effects of cigarette smoking on the endothelium

A.D. Blan and C.N. McCollum, *Department of Surgery, Withington Hospital, Manchester, UK*

Cigarette smoking is associated with cardiovascular disease The mechanism may involve damage to the endothelial cell (EC). We examined the effects of serum from smokers and non-smokers (hospital and laboratory staff) on markers of EC integrity and function von Willebrand factor antigen (vWFAg), a specific product of EC, was measured by enzyme-linked immunosorbent assay, and EC cytotoxicity *in vitro* was estimated by an isotope release assay Changes in growth patterns of EC in culture were determined by assay of DNA content and by production of prostacyclin (radioimmunoassay).

vWFAg was raised in smoker's serum (113 ± 58 IU dl^{-1}, $n=62$) relative to that in non-smoker's serum (81 ± 29, $n=65$, $P<0{\cdot}01$, Mann–Whitney). Increased levels correlated with both daily consumption of cigarettes ($r=0{\cdot}26$, $P<0{\cdot}05$) and number of years smoking ($r=0{\cdot}46$, $P<0{\cdot}001$, Spearman) Smoker's serum was no more cytotoxic to EC *in vitro* than serum from non-smokers ($10{\cdot}6 \pm 2{\cdot}4$, $10{\cdot}7 \pm 4{\cdot}2$). The effects of acute smoking was tested by taking serum immediately before and after a cigarette. Serum was cytotoxic after smoking ($9{\cdot}1 \pm 2{\cdot}9 - 10{\cdot}5 \pm 2{\cdot}6$, $n=11$, $P<0{\cdot}05$, Wilcoxon) but vWFAg was not increased ($110 \pm 34 - 115 \pm 38$) Smoker's serum had an adverse effect on growth rates of EC after 6 days in culture (1240–1585 ng DNA, $P<0{\cdot}05$, analysis of variance), and EC cultured with smoker's serum produced lower levels of prostacyclin ($30{\cdot}1$–$54{\cdot}0$/ng/ml/10^6 cells, $P<0{\cdot}05$, Wilcoxon)

We have measured a variety of indices of EC integrity and function, both *in vitro* and *in vivo* These clearly show that cigarette smoking has a harmful effect on the endothelium by reducing growth rates, inhibiting production of prostacyclin and exerting a cytotoxic effect on endothelial cells

Carotid endarterectomy without angiography: safety and efficacy

D.A. Ratliff, P.D. Fry, D.L. Doyle, Y. Hsiang and M. Fragoso, *University Hospital, Vancouver, Canada*

Patients undergoing carotid endarterectomy are conventionally investigated by cerebral angiography before surgery. In recent years duplex scanning has been shown to be an extremely accurate technique in the diagnosis of carotid artery disease and it is non-invasive We now have sufficient confidence in duplex scanning in our department that we feel able to proceed to carotid endarterectomy without angiography in the majority of patients.

We report our experience of 108 consecutive carotid endarterectomies in 100 patients from 1 October 1986 to 31 March 1990 There were 55 males and 45 females of mean age 68 years. Of patients, 80 per cent were symptomatic and 70 (65 per cent) were investigated by duplex scanning of the carotid arteries and computerized tomography scan of the head only Pre-operative cerebral angiography was felt to be indicated in the remaining 35 per cent of cases. An intraoperative shunt was used in 84 per cent of cases

The combined permanent neurological morbidity and mortality was 4·6 per cent. One patient died from adult respiratory distress syndrome without neurological complication (0·9 per cent) Four patients developed ipsilateral peri-operative strokes, three of carotid and one of retinal distribution (3·7 per cent). There was no difference in morbidity and mortality in those patients who did not have pre-operative angiography and those who did

We feel that these results confirm that carotid endarterectomy can be safely and effectively performed without angiography in many patients Pre-operative cerebral angiography may be reserved for selected patients, particularly those with complex symptoms or evidence of widespread disease, or where there is any doubt about the result of the duplex scan

Durability of carotid endarterectomy assessed by duplex sonography

Allan R. Downs, *University of Manitoba, Winnipeg, Manitoba, Canada*

From 1976 to 1989, 245 carotid endarterectomies were performed on 208 patients by the author for carotid artery stenosis. The indications for operation were: asymptomatic 8 per cent, amaurosis fugax 14 per cent, transient ischaemic attack (TIA) 23 per cent, completed minor or major stroke 27 per cent, anaurosis plus TIA, stroke or vertebrobasilar insufficiency (VBI) 22 per cent and TIA and VBI 3 per cent. All patients were operated upon using general anaesthesia. A temporary shunt was used in 40 per cent based on stump pressure < 50 mmHg, a recent completed stroke or contralateral occlusion. Vein patch closure was used in 12 per cent. Completion angiography was performed in all patients There was one postoperative death due to pneumonia (0·4 per cent). There were three peri-operative strokes (1·2 per cent) with a permanent major neurological deficit. There were four peri-operative strokes with minor permanent deficit in three patients (1·2 per cent). Two postoperative occlusions were treated successfully by thrombectomy. Follow-up ranged from 6 to 144 months There have been 69 late deaths, three due to a stroke in the contralateral hemisphere Carotid duplex sonography has been performed on 136 patients A total of 168 examinations have been performed between 3 months and 12 years postoperatively. Twelve arteries have significant recurrence of disease· moderate (50–79 per cent) in nine, severe (80–99 per cent) in one, and occlusion in two. Only one stenosis was demonstrated prior to 3 years follow-up These results demonstrate that carotid endarterectomy can be performed with a low peri-operative morbidity and the late recurrence of stenosis is very low

Long-term duplex follow-up after carotid endarterectomy: research or patient care?

R.J Th.J. Welten, B.C. Eikelboom and R.G.A. Ackerstaff, *Sint Antonius Hospital, Nieuwegein, The Netherlands*

Since the introduction of duplex scanning in our institution in 1980, we have followed all patients after carotid endarterectomy 3 months postoperatively and once a year thereafter. This study investigates what has been learnt from this policy and whether it is necessary for good patient care.

A total of 920 operations were performed from 1971 to 1989 Cumulative 10-year survival was 56 per cent, compared to 75 per cent in an age- and sex-matched normal population Cumulative freedom of stroke at 7 years was 89 per cent. Late stroke occurred in 65 per cent of cases on the operated side. There was no correlation between late stroke and restenosis. The overall 1 and 5 year cumulative restenosis rates were 10 and 16 per cent Most restenoses developed within 6 months and occurred significantly more often in women, after closure without a patch, and when residual lesions were present The first postoperative year is characterized by dynamic changes in the endarterectomized segment with progression as well as regression of lesions. In non-operated contralateral arteries, disease progression to stenosis > 50 per cent was seen in 45 per cent of cases after 5 years.

Serial duplex scanning provides important information about carotid disease, but it is not essential for good patient management in the assessment of evidence that endarterectomy is indicated for asymptomatic (re)stenosis

Long-term clinical and duplex results following carotid endarterectomy

R Bell, C.C.R. Bishop, Kate Somerville and N.L. Browse, *St Thomas' Hospital, London, UK*

The aim of carotid endarterectomy is to abolish pre-operative symptoms and to prevent subsequent stroke A 5–8 year follow-up study was conducted on 88 patients who had undergone 108 carotid endarterectomies by a single surgeon over a 3-year period (July 1982–July 1985). Sixteen patients were deceased and twelve were lost to follow-up leaving 60 patients (39 men, 21 women) with a mean age of 61 years (41–71 years) for assessment of 70 carotid endarterectomies (10 bilateral) at a mean of 6·5 years following operation.

Patients were questioned about symptoms and duplex scanning (Acuson) of both carotid arteries performed. Duplex scanning revealed 6 (8 per cent) total occlusions and 11 (16 per cent) severe stenoses (reduction >50 per cent diameter) in the 70 operated arteries and disease progression in 11 (22 per cent) of 50 unoperated contralateral arteries. Four patients developed ipsilateral hemisphere stroke of which two were in the immediate postoperative period (one death) and the other two occurred at 1 month and 12 months. Three of these strokes were associated with occlusion of the endarterectomized vessel. Eight patients had ipsilateral transient ischaemic attacks, two associated with widely patent arteries, two with mildly stenosed arteries, three with severely stenosed arteries and one following total occlusion Contralateral transient ischaemic attacks occurred in three patients.

This study demonstrates that despite a 24 per cent restenosis or occlusion rate, 93 per cent of patients remained stroke free and 78 per cent experienced no further neurological events following carotid endarterectomy.

Practical implications of intra-operative monitoring with transcranial doppler ultrasonography during carotid endarterectomy

R. Naylor, A. Wildsmith, J. McClure, A. Jenkins and V. Ruckley, *Departments of Vascular Surgery and Anaesthetics, Royal Infirmary, Edinburgh, UK*

We have employed continuous monitoring of middle cerebral artery (MCA) velocity using transcranial doppler ultrasound (TCD) in 30 consecutive patients as an adjunct to our routine methods of cerebral monitoring during carotid endarterectomy. Our aim was to see whether TCD provided any new information that might influence operative or anaesthetic practice

TCD demonstrated a higher frequency of intra-operative embolization (air/platelet) than had been otherwise anticipated; during carotid mobilization (3 per cent), during carotid clamping (3 per cent), following shunt insertion (40 per cent) and following final restoration of flow (27 per cent). In one case, there was embolic occlusion of the MCA, the remainder were minor and asymptomatic. TCD immediately identified inadvertent shunt kinking in one patient and overinflation of the shunt balloon in a second. Two patients suffered immediate postoperative (transient) neurological deficits and TCD was able to identify the probable aetiology in both (MCA embolus 1, haemodynamic 1) and avoid urgent re-exploration. We also observed that preliminary flushing of the arteriotomy site through the external carotid artery could cause MCA embolization via reversed flow in the opthalmic artery. A further finding was loss of cerebral autoregulation, when using volatile anaesthetic agents, which has implications for intra and postoperative blood pressure control.

TCD has therefore enabled us to identify (potentially) high risk phases associated with embolization and problems with shunt deployment, and our operative technique has been revised accordingly. In addition, TCD offers the potential for identifying underlying causes of intra-operative neurological deficit and avoiding unnecessary early re-exploration.

Contralateral stenosis and stump pressure measurements: relevance to carotid surgery

P. Burke, E. Tadros, E. Prendiville, M.P. Colgan, D. Moore and G. Shanik, *Department of Vascular Surgery, St James' Hospital, Dublin, Ireland*

Carotid endarterectomy under local anaesthesia allows monitoring of mental status perioperatively with reduced emphasis on angiography and stump pressures. Our experience with this change is presented.

Over the past 7 years, we have performed 208 carotid endarterectomies, 32 under general anaesthesia and the remaining 176 under local anaesthesia. Stump pressure measurements in 115 patients and angiographic findings on all patients were prospectively recorded.

There were no deaths However, five patients (2·4 per cent) suffered a perioperative stroke and seven (3·4 per cent) a transient ischaemic attack. An additional ten patients obtunded while the internal carotid artery was clamped with complete resolution on revascularization. Two of the five strokes occurred in patients under general anaesthesia while the remaining nine strokes or transient ischaemic attacks occurred following local anaesthesia. There was no change in mental status in these patients during surgery.

Mean stump pressure was significantly lower in the 21 patients suffering a perioperative event ($36{\cdot}6 \pm 21{\cdot}9$ mmHg versus $56{\cdot}3 \pm 27{\cdot}9$ mmHg, $P<0{\cdot}02$, Student's t test) as well as in the 58 patients with a contralateral stenosis $\geqslant 80$ per cent, irrespective of ipsilateral stenosis ($40{\cdot}2 \pm 20{\cdot}4$ versus $58{\cdot}5 \pm 28{\cdot}7$ mmHg, $P<0{\cdot}002$, Student's t test) Perioperative complications occurred more frequently in patients with $\geqslant 80$ per cent contralateral stenosis (11/58 versus, 10/150, $P>0{\cdot}02$, Fisher's exact test). Nine of the 21 perioperative events were identified by assessment of mental status alone Using the combination of stump pressure $\leqslant 35$ mmHg and/or contralateral stenosis $\geqslant 80$ per cent. 15 could be predicted. We conclude that angiographic assessment and stump pressure measurements are important markers of perioperative risk and urge their continued use in carotid endarterectomy under local anaesthesia.

Prospective carotid patch/non-patch study

C. Ranaboldo*, A. Barros D'Sa†, P. Bell‡, M. Perry∞ and A. Chant*, *Joint Vascular Research Group, *Southampton, †Belfast, ‡Leicester, ∞Portsmouth, UK*

A prospective randomized trial has been performed to evaluate patch angioplasty in carotid endarterectomy. Two hundred and thirteen patients were recruited (148 male, 65 female) with a mean age of 65·5 years (range 45–82 years) Of these 109 were allocated to the patch group. Three patients died postoperatively from myocardial events (one patched, two non-patched). At 1 year, 14 other patients had died

Following surgery, five patients suffered transient ischaemic attacks, none of which delayed discharge. Postoperative bleeding requiring re-exploration occurred in six individuals (four patched, two non-patched) There were eight potentially serious neurological problems after operation (two patched, six non-patched). Of these, four patients, all non-patched, were re-explored with the clot being removed and the arteriotomy then closed with a patch All four patients made good long-term recoveries.

So far 82 per cent of patients have completed objective follow-up assessment with a duplex scanning. Of these, ten have developed a stenosis of > 50 per cent (four patched, six non-patched), while a further ten have occluded the operated vessel (two patched, eight non-patched).

The indications for carotid endarterectomy remain uncertain As a prophylactic procedure any measure that reduces the associated mortality and morbidity must be considered We conclude that patch angioplasty with carotid endarterectomy reduces immediate postoperative complications, while vessel restenosis and occlusion rates at 1 year are also reduced with the use of a patch during the closure of the carotid arteriotomy.

Carotid endarterectomy in the UK and Ireland (1989)

J.A. Murie and P.J. Morris*, *Royal Infirmary, Edinburgh and *John Radcliffe Hospital, Oxford, UK*

Out of 309 questionnaires about carotid endarterectomy (CE), which were sent to all surgeons in the UK and Ireland who might include such surgery in their practice, 298 (96 per cent) were returned. One hundred and ten (37 per cent) of the 298 surgeons performed at least one CE in 1989; 67 carried out $\leqslant 10$ and 43 carried out >10 CEs. In total, these 110 surgeons performed 1417 operations in 1989, a situation which has changed little over the 5 years since a previous survey, which showed that 96 surgeons performed 1374 CEs in 1984[1]. The indications for CE in order of frequency remain transient ischaemic attack, minor stroke and stroke. Operation was hardly ever performed for asymptomatic carotid bruit. By 1989 almost every surgeon assessed prospective patients in the first instance using a technique less invasive than conventional angiography: duplex scanning was used 'always or sometimes' by 69 per cent, intravenous digital subtraction angiography by 45 per cent and intra-arterial digital subtraction angiography by 39 per cent. The most dramatic investigative change, however, occurred in the requirement for conventional angiograms[2] before operation These were required by 89 per cent of surgeons in 1984, but by only 45 per cent in 1989 While there was little change in the widespread use of general anaesthesia and the frequency of shunt usage, closure of the arteriotomy with a patch has become popular, 20 per cent 'always or often' used a patch in 1984 compared with 42 per cent in 1989.

The significant changes in the practice of CE in the UK and Ireland over the last 5 years are: (a) preliminary investigations have become less invasive, (b) conventional angiograms are now less often required, and (c) patch closure of the arterotomy has become popular. The overall number of operations, however, has remained fairly static and is relatively low for a population of 60 million.

1 Murie JA, Morris PJ Carotid endarterectomy in Great Britain and Ireland. *Br J Surg* 1986; 73: 867–70.

2. Murie JA, Morris PJ. Arterial assessment before carotid endarterectomy *J Cardiovasc Surg* 1987; **28** 516–19.

Abnormal response of digital blood flow to acute vibration in patients with vasospastic disease

P. Kent, G. Williams and R.C. Kester, *Seacroft Hospital, Leeds, UK*

Fifteen patients with primary Raynaud's, 13 patients with vibration-induced white finger (VWF) and 14 controls were exposed to sine-wave vibration of 0·15 mm amplitude and 40, 80 and 120 Hz frequency. Baseline digital blood flow was measured in the middle digit of each hand using venous occlusion strain gauge plethysmography The right middle digit was vibrated for 1 min. Subsequent measurements were taken from both vibrated and non-vibrated digits

Vibration at 40 Hz caused a significant decrease in flow in the vibrated digits of the control group only ($P < 0\cdot01$, Wilcoxon). Vibration at 80 Hz showed a significant decrease in blood flow in the vibrated digits of both the control* and the VWF** groups and also in the non-vibrated digits of the VWF** group ($^*P < 0\cdot005$, $^{**}P < 0\cdot05$, Wilcoxon). Vibration at 120 Hz significantly decreased blood flow in the vibrated digits of control*, VWF* and Raynaud's* groups The Raynaud's non-vibrated digits also had decreased flow** ($^*P < 0\cdot001$, $^{**}P < 0\cdot005$, Wilcoxon)

These results imply that patients with established vasospastic disease are less sensitive to the direct effects of acute vibration than controls. The results also imply that vibration at 40, 80 and 120 Hz affects digital blood flow in controls through a local mechanism Vibration at certain frequencies appears to modulate blood flow in patients with vasospastic disease by acting through central mechanisms

Profunda femoris artery as outflow in anatomical and extra-anatomical bypass for aortofemoral occlusive disease

E. Prendiville, P. Burke, M.P. Colgan, B. Wee, D. Moore and G. Shanik, *Department of Vascular Surgery, St James' Hospital, Dublin, Ireland*

The profunda femoris artery (PFA) may be used in bypass surgery for aortoiliac occlusive disease when significant common femoral artery (CFA) outflow obstruction co-exists. Long-term results of PFA bypass are poorly documented Over an 11 year period, 375 limbs were revascularized in 194 patients, 285 by aortofemoral (A-Fem) and 90 by axillofemoral (Ax-Fem) bypass. The CFA was the outflow vessel in 189, proximal PFA in 144 and mid/distal PFA in 42. Indications and results are shown below

Bypass	No	Mean age (years)	Critical ischaemia (%)	Cumulative patency (%) at		Limb salvage (%) at	
				3 years	5 years	3 years	5 years
A-Fem	285	63	69	98 ± 1	93 ± 3*	96 ± 2	94 ± 3
A-CFA	151	62	65	99 ± 1**	96 ± 2	98 ± 1	98 ± 2
A-PFA	134	64	74	96 ± 2†	91 ± 6	94 ± 3	90 ± 6
Ax-Fem	90	71	91	83 ± 8	72 ± 12*	90 ± 5	83 ± 7
Ax-CFA	38	74	89	89 ± 12**	89 ± 14	100	100
Ax-PFA	52	69	92	79 ± 10†	63 ± 16	83 ± 10	83 ± 10

$^*P < 0\cdot005$, $^{**}P < 0\cdot02$, $^{\dagger}P < 0\cdot05$, log rank test

Angiograms and non-invasive studies showed more significant infra-inguinal disease in the Ax-Fem group and in both groups where the PFA was used for outflow. The number of concomitant or subsequent distal bypasses required to maintain limb salvage was similar in the CFA and PFA groups. The profunda-popliteal collateral index did not predict graft failure or the need for distal bypass. Proximal and mid/distal A-PFA showed no difference in cumulative patency (96 ± 3 versus 95 ± 7 per cent at 3 years) or limb salvage (94 per cent per group) and results were similar to CFA bypass.

Although Ax-Fem resulted in excellent limb salvage, A-Fem showed superior long-term patency. A-Fem is the operation of choice in medically fit patients, and where significant CFA outflow obstruction exists, proximal or mid/distal PFA bypass should be performed, thereby reducing the need for distal bypass procedures

Comparison of clinical, vascular laboratory and angiographic determination of amputation levels

Th A.A. van den Broek and J.A. Rauwerda, *Free University Hospital, Amsterdam, The Netherlands*

Although amputation surgery still suffers from a complication rate of up to 30 per cent there seems to be hardly any improvement in adequate preoperative prediction of healing. We therefore studied prospectively a new, easy and quick non-invasive technique to assess skin perfusion pressure, together with other vascular laboratory techniques, clinical and angiographic criteria.

Fifty-three patients with amputations of the lower limb were entered in the study. Clinical criteria were presence or absence of necrosis with or without purulent discharge, temperature and colour of skin, and pulses. Vascular laboratory results were pulse volume registrations (PVR), doppler pressures and photoplethysmographic skin perfusion pressures (PPGSPP). Forty-five patients completed the evaluation

Skin conditions and pulses did not prove of predictive value. Doppler and PVR studies also did not correlate with healing. The technique of PPGSPP measurement, however, proved very reliable in amputation level selection, especially if measured anteriorly at the level of amputation · ($P < 0\cdot0001$, $r = 0\cdot83$). Angiographic scoring also correlated significantly ($P = 0\cdot0016$).

Clinical diagnosis for the selection of the amputation level seems insufficient In the absence of reliable non-invasive tests, angiography could be used. PPGSSP will enable the surgeon to minimize complications after amputation by determining an optimal level

'Skew flap' versus the Burgess long posterior flap – a prospective randomized trial

Messrs. . Reynolds, Hind, Lindsay, Nash and Callum, *City Hospital and Royal Infirmary, Derby and Artificial Limb Appliance Centre, Nottingham, UK*

In a prospective randomized trial, the times to wound healing, prosthesis fitting and eventual mobility were compared between myoplastic skew flap (SF) and Burgess long posterior flap (LPF) below knee amputation. Fifty-four amputations were performed in 51 patients (SF 30; 18 men, 9 women) (LPF 24; 15 men, 9 women) of median age 73 years, range 39–95 years, and all patients suffered from critical ischaemia. Of patients, 62 per cent were diabetic. Primary wound healing occurred in 17 (56 per cent) SF amputations, and 11 (46 per cent) LPF (n s.). Failure, requiring proximal amputation, occurred in 6 SF and 4 LPF amputations. Mortality at 30 days was 8 per cent and there was no difference between the two groups Median time to full healing of SF was 14·5 (10–210) days, compared with 21·5 (10–150) days for LPF ($P < 0\cdot05$). Time to fitting of a patella tendon bearing prosthesis was significantly shorter in SF patients, compared to LPF (28 versus 52 days, $P < 0\cdot05$). Mobilization time was also significantly shorter in SF patients (median 6 weeks, range 4–32), compared with LPF patients (13, 5–49, $P < 0\cdot01$).

The failure rate, requiring higher amputation, of 20 per cent in each group is higher than previously reported, but SF amputation would appear to have an advantage with respect to both healing time and earlier mobility.

First experiences with magnetic resonance spectroscopy to determine the viability of gastrocnemius muscle in lower extremity ischaemia

M.P H. Crolla, J. van der Grond*, W. ten Hove*, W.P.Th.M. Mali* and Th.J.M.V. van Vroonhoven, *Department of Surgery and *Department of Radiodiagnosis, University Hospital of Utrecht, The Netherlands*

In major lower extremity amputation the most distal amputation level is preferred However, predicting wound healing at a given level is difficult. Many non-invasive and invasive tests have failed to be of predictive value because these techniques either measure ischaemia indirectly or at non-essential sites. Magnetic resonance spectroscopy (MRS) can study cell metabolism in a non-invasive, direct way. ^{31}P-MRS can measure the high-energy phosphate metabolites adenosine triphosphate (ATP), phosphocreatine (PCr) and inorganic phosphate (P_i) in human tissue. In ischaemia, PCr stores are depleted to maintain ATP levels and P_i levels rise PCr/P_i ratio could reflect the energy state and thus the viability of muscle. In our study ^{31}P-MRS was performed on a 1,5 T whole body system. With a 4 cm diameter, doubly tuned (^{1}H-^{31}P) surface coil ^{31}P-MR spectra at rest were obtained at 15 cm above, 12 cm below and 20 cm below the knee joint In 17 healthy, asymptomatic volunteers, age 20 to 75 years, the PCr/P_i ratio always exceeded 8·0, average 8·5. Twenty-six patients were classified into six groups, based on clinical symptoms In mild claudication (group 1), no difference in the PCr/P_i ratio from the healthy volunteers could be measured at rest. In more severe claudication, the PCr/P_i ratio decreased but no significant differences were found between groups 2, 3 and 4. In group 5 and 6, the PCr/P_i ratio reached a very low level All legs in patients with a PCr/P_i ratio <2 had to be amputated. In conclusion, MRS seems to offer a non-invasive tool to measure the energy state in human muscle *in vivo*.

Evaluation of tourniquet ambulatory venous pressure as a selective test of superficial and deep venous function

P.E. Kiely, *Bon Secours Hospital, Cork, Ireland*

A test is needed which will differentiate quantitatively between venous insufficiency (VI) due to incompetent superficial veins and VI originating in the deep veins This study provides a comprehensive assessment of tourniquet ambulatory venous pressure AVP(T), in selectively identifying that component of VI resulting from retrograde superficial blood flow.

One hundred and seventy limbs had ambulatory venous pressure (AVP) measured without and with a superficial tourniquet just below the knee. Of these limbs, 140, including 31 with objective evidence of deep venous dysfunction, had the measurements repeated after surgical removal of all incompetent superficial veins. Pre-operatively in each of these limbs there was a major reduction in AVP on application of a tourniquet whereas after operation the tourniquet had no effect This indicates that the tourniquet had a profound effect on retrograde superficial flow, AVP > AVP(T), but did not alter deep venous function, AVP after operation = AVP(T) after operation In the vast majority, the tourniquet was accurate in identifying that component of VI caused by retrograde superficial flow, as in these limbs AVP(T) = AVP after operation. This prediction held true whether the deep veins were normal or abnormal

In 30 limbs with extensive postphlebitic deep vein damage the tourniquet did not identify haemodynamically significant superficial incompetence, AVP = AVP(T). VI in these limbs was judged to be entirely located in the deep veins, and in fact eight were shown to have no superficial vein incompetence on doppler evaluation.

AVP without and with a superficial tourniquet provides an overall estimate of the degree of venous insufficiency in the lower limb and accurately quantifies those elements of the insufficiency which are located in the superficial and deep systems.

Economic options and decision making in the ischaemic lower limb

N.J. Chesire, M.A. Noone, L. Davies*, M. Drummond* and J.H.N. Wolfe, *St Mary's Hospital, London and *The Health Services Management Centre, Birmingham, UK*

Arterial recontruction may be expensive and does not always prevent amputation. Health economists have compared resource use and cost of 314 primary reconstructions for ischaemia (79 per cent proximal reconstructions including femoropopliteal, 21 per cent distal reconstructions to calf vessels) and 62 amputations. In addition, clinical outcome in terms of mobility, rehabilitation, re-housing and complications have been assessed and costed.

During the 1–6 year follow-up period, 63 per cent of more proximal reconstructions were uncomplicated, 28 per cent required further surgery to save the limb (average 1·9 further operations/patient) and 9 per cent required intervention resulting in major amputation. Of the femorocrural group, 43 per cent remained uncomplicated, 24 per cent required re-operation without amputation (average 2·3 further operations/patient) and 33 per cent eventually required amputation. Considering all amputations performed, major revision (below to above knee) was necessary in 15 per cent of cases. Such probabilities have been used to construct a clinical decision tree

The average primary costs of reconstruction and amputation were £1650 and £3050 respectively A policy of reconstruction, including the cost of secondary intervention, produced in-patient costs of £3240. A policy of primary amputation cost £3920 (21 per cent more expensive). In addition, amputees incur significant community costs of between £6000 and £21 000 related to care of immobile elderly patients (34 per cent of amputees are wheel-chair bound or bed-ridden).

Few doubt the value of proximal reconstruction but, in this study, operation to crural vessels was economically effective. Of greater value is the decision tree analysis which can be used by any unit to aid clinical decisions and enable comparison between various units and European health care systems.

Vein graft screening: a prospective study of aetiological factors

A.P. Moody, P.R. Edwards and P.L. Harris, *Broadgreen Hospital, Liverpool, UK*

In a prospective series of 74 femoropopliteal vein grafts, 22 strictures were identified by duplex scanning in 18 grafts (24 3 per cent) A selective policy of treatment by percutaneous transluminal angioplasty improved cumulative patency by 12 per cent in the first year compared with a retrospective series of 214 comparable grafts from the same unit The benefits of screening and prophylactic treatment are clear but progress in the management of strictures depends on an improved knowledge of the aetiological factors involved

Seventy four vein grafts were marked using surgical clips at sites of all valves, tributaries, clamps and venotomies, since these have all been suggested as potential sources for graft strictures. A total of 377 valves, 681 tributaries, 15 clamps, and 2 venotomies were identified on follow-up intravenous digital subtraction angiograms and duplex scanning Of the 22 strictures detected by screening, only one coincided with a specific marked area (a valve site) Duplex examination in 34 *in situ* grafts identified 10 residual valve cusps in 7 grafts In none of these was there any evidence of turbulence or flow disturbance.

In conclusion, there is no correlation between valve sites, tributaries, clamp sites or residual valve cusps and the development of vein graft strictures. The cause is likely to be either pre-existing fibrosis in the vein graft wall, which requires better vein selection, or de-endothelialization of sections of vein during the harvesting procedure, leading to increased platelet deposition. This factor could be mitigated by better vein handling or by pharmacological intervention.

Balloon dilation of graft stenoses – reasons for failure

P.R. Taylor, D. Gould, P. Harris, A. Al-Kutoubi and J.H. Wolfe, *St Mary's Hospital, London and Broadgreen Hospital, Liverpool, UK*

It is now well established that graft-related stenoses occur in ≈20 per cent of grafts. Balloon dilatation of these is an attractively simple form of treatment but is associated with variable results We have therefore amalgamated the experience of two centres to assess the reasons for failure.

Twenty-four stenoses in 21 grafts in 21 patients were treated over the last 6 years. The proximal anastomosis was to the common femoral artery in 18 and the superficial femoral artery in three The distal anastomosis was to the popliteal in 16 and the crural vessels in 5 Thirteen grafts were *in situ* vein, seven were reversed vein and one polytetrafluoroethylene. Fourteen stenoses (58 per cent) were related to the distal anastomosis, five (21 per cent) to the body and five (21 per cent) to the proximal anastomosis. Eighteen (75 per cent) were <1 cm in length, two were between 1–2 cm and four were >3 cm Eighteen stenoses (75 per cent) were successfully dilated without any residual stenosis. Three (13 per cent) had slight residual stenosis and one (4 per cent) had a marked residual stenosis Two (8 per cent) occluded immediately during the procedure Of the 21 grafts, 11 (52 per cent) remain patent at an average follow-up of 22 months Five (24 per cent) occluded late at an average of 12·6 months Two grafts re-stenosed at an average of 5 months and, together with the stenosis which failed to dilate, underwent tertiary procedures Three of the four stenoses >3 cm subsequently occluded at a mean 6 months despite an initially successful dilatation with no stenosis Of the 15 grafts with <1 cm stenosis which were successfully dilated, only two occluded (mean 22·5 months) and two re-stenosed (mean 5 months) – a patency rate of 73 per cent at 22 months.

Graft-related stenoses measuring 1 cm or less can be successfully treated with balloon dilatation and, in our experience, are associated with reasonable patency rates. Furthermore, the results are durable and we have not seen the higher re-stenosis rates reported in some series However, the results for longer stenoses are poor and these should be corrected by open surgery

Prospective randomized comparison of *in situ* and reversed grafts for femoropopliteal and infrapopliteal bypass

P.R. Edwards, P.L. Harris, K. Wengerter*, F. Veith* and G. Shanik$^+$ *Broadgreen Hospital, Liverpool, UK (*New York, $^+$Dublin)*

The results of a previously reported randomized study of *in situ* and reversed vein grafts for femoropopliteal bypass showed no difference in patency rates between these two types of graft up to 3 years after operation. Subsequent analysis indicates that no significant advantage exists for either of the grafts up to 5 years after operation. Of the factors affecting outcome, minimum diameter of the grafts had greatest influence, the cumulative patency <4 mm being 36 per cent at 5 years compared to 76 per cent for those >4 mm ($P<0{\cdot}002$) Small vein size affected patency adversely for *in situ* and reversed grafts equally. A separate study has been undertaken for infrapopliteal bypasses in conjunction with two other centres, Dublin and New York. One hundred and twenty five patients undergoing bypass surgery to the calf or pedal arteries with ipsilateral saphenous vein grafts were randomly allocated to the *in situ* or reversed operation To date, no significant difference in patency has been demonstrated between the two groups. Cumulative patency rates for both the femoropopliteal and infrapopliteal grafts are shown below

			Time after graft (years)					
Study	Graft	No	1	2	3	4	5	
Femoro-popliteal	*In situ*	101	80	74	71	69	64	n.s.
	Reversed	114	85	75	70	66	62	
Femoro-infrapopliteal	*In situ*	63	80	72	72	–	–	n.s.
	Reversed	62	76	68	68	–	–	

The data from these two studies indicate that similar patency rates can be expected from *in situ* and reversed vein grafts in both femoropopliteal and infrapopliteal reconstructions There is evidence that the main determinant of the outcome from these operations is the quality of the saphenous vein

Valvulotome-induced smooth muscle injury in femorodistal vein grafts

R.D. Sayers, P.A.C. Watt*, P.R.F. Bell and H. Thurston*, *Department of Surgery and *Medicine, Leicester University, Leicester, UK*

In infra-inguinal bypass, autologous saphenous vein remains the best conduit with patency rates superior to prosthetic alternatives Recent studies of reversed vein grafts have shown that careful handling of the saphenous vein is necessary to maintain a functionally intact vessel. It has been suggested that damage to the vein may lead to intimal hyperplasia, a major factor in late graft failure. We have studied the effect of valvulotome injury on contractility of the smooth muscle of *in situ* femorodistal vein grafts

Veins from 16 patients were studied after dissection only or after the passage of a valvulotome. The vessels were placed in a heated bath (37°C) containing Krebs' solution and gassed with 5 per cent CO_2/95 per cent O_2. One end of the vein was fixed and the other connected to a force transducer measuring isometric tension. Vessels were set to a tension that would elicit a maximum contraction to noradrenaline (control $2{\cdot}50\pm0{\cdot}27$ g; valvulotome $1{\cdot}67\pm0{\cdot}44$ g). A cumulative dose response curve to noradrenaline (10 nM to 10 μM) was performed in the presence of 1 μM cocaine. The maximum response elicited for control veins was $10{\cdot}86\pm1{\cdot}35$ g compared to $3{\cdot}39\pm1{\cdot}35$ g in the valvulotome group ($P<0{\cdot}01$). The ED_{50} response in the control group was $0{\cdot}056\pm0{\cdot}016$ μM with $0{\cdot}894\pm0{\cdot}369$ μM in the valvulotome group ($P<0{\cdot}05$).

These results suggest that the current use of a valvulotome not only renders the valves incompetent but seriously damages the function of the smooth muscle layer This may be an important factor in the cause of late graft failure due to intimal hyperplasia

Intraoperative angioscopy for the assessment of infrainguinal bypass grafts

P.A. Stonebridge and A. Miller, *Harvard-Deaconess Surgical Services, New England Deaconess Hospital, Boston, USA*

To date we have performed 411 intraoperative angioscopies. Of these 342 were to monitor infrainguinal bypass grafts (77 femoropopliteal and 265 distal bypasses) and 94·4 per cent for limb salvage. Eighty per cent of the patients were diabetic. The bypass conduit was vein in 321 (*in situ* 192, non-reversed 89, reversed 40), polytetrafluoroethylene (PTFE) in 8 and PTFE-vein in 13. To allow angioscopic visualization the blood was displaced by normal saline delivered by a dedicated irrigation pump (mean irrigation fluid volume/case = 404 ml). A 1·4 mm outer diameter (OD) angioscope was used most frequently in distal bypasses (78 per cent). In femoropopliteal bypasses a 2·2 mm OD angioscope with mechanical steering was used in 40 per cent of cases and 1·4 mm OD in 53 per cent. The distal anastomosis was fully visualized in 94·5 per cent of cases and the graft in 98 per cent. Residual competent valve cusps were identified in 20 per cent of *in situ* and 9 per cent of non-reversed vein grafts. Unligated tributaries were detected and ligated in 38 per cent of *in situ* grafts In all, 184 clinical decisions were made on the basis of intraoperative angioscopy. The early (<30 days) occlusion rate was 8·2 per cent. Perioperative mortality was 4·1 per cent. There wre no significant complications related to the angioscopy procedure. New endovascular pathological findings were noted. Intraoperative angioscopy provided the ability to detect and immediately correct defects within bypasses Routine intraoperative angioscopy appears to be a safe, reliable and effective method of intraoperative graft monitoring

Impedance analysis for prediction of the outcome following femoropopliteal/distal bypass

M G. Wyatt, W.G. Tennant, R.N. Baird and M. Horrccks, *Vascular Studies Unit, Royal Infirmary, Bristol, UK*

Impedance analysis is a new non-invasive method of graft surveillance which can detect both graft and run-off stenoses following femoropopliteal/distal (FPD) bypass[1].

In a series of 106 patients undergoing FPD for critical ischaemia, impedance scores (mean (95 per cent confidence interval)) were significantly higher in 'at risk' grafts (graft or run-off stenoses >50 per cent on biplanar intra-arterial digital subtraction angiography: 0·58 (0·41–0·75)*) when compared with controls (no stenoses: 0·36 (0·30–0·42), $^{*}P>0{\cdot}001$). An impedance score of >0·45 successfully identified 53 of 56 (95 per cent) 'at risk' grafts. Twenty five of these patients (45 per cent) had normal post-stressed ankle/brachial indices (>0·8) and duplex scanning failed to identify 31 of 43 distal anastomotic/run-off related lesions

No action was taken in 37 'at risk' grafts and 17 of these, all with an impedance score of >0·5, have occluded. Secondary procedures have been performed in 19 patients (16 balloon angioplasty, 3 operative). In 13 grafts, impedance scores returned to normal (<0·45) following intervention and all remain patent. Of the six grafts in which the impedance score remained unchanged, three have occluded, one underwent further revision and two remain 'at risk'. All 50 control grafts remain patent except one which occluded following an intra-arterial digital subtraction angiogram.

These results confirm the value of impedance analysis in the detection of graft and run-off stenoses following FPD. A graft with a high impedance is more likely to fail, but patency can be preserved following successful intervention. This non-invasive test is repeatable and reproducible and is now in routine use in our laboratory for the detection of 'at risk' grafts prior to failure

(*Mean ± 95 per cent confidence interval, Mann–Whitney *U* test).

1 Computer-assisted impedance analysis (CAIA)· a new method to detect 'at risk' femorodistal grafts. *Association of Surgeons of Great Britain and Ireland, Programme and Abstracts* 1990, 96

Early experience using a biopolymeric graft (St Jude)

M A. Walker, J.G.R. Cumming, P.J. Cullen, G.H. Dunstone and W.F. Walker, *Dryburn Hospital, Durham and Ninewells Hospital, Dundee, UK*

Where there is no suitable saphenous vein for femoropopliteal bypass, previous experience with synthetic grafts and biografts (Dardik) has proved disappointing. A biograft has become available with an increased tensile strength and decreased thrombogenicity due to a negatively charged wall We report our initial experience of its use.

Ninety femoropopliteal grafts have been implanted in patients in whom the vein was found to be unsuitable. All patients were suffering from disabling claudication on flat ground, rest pain or incipient gangrene. The first graft was inserted in July 1988 and to date a total of 72 patients have reached 6 months or more after grafting with a 76 per cent patency rate at this time. Seventeen grafts have required thrombectomy Of the 14 grafts which have remained blocked, 3 patients have required amputation and 3 have died from myocardial infarction. One patient has had a functioning graft removed because of infection and one with very poor distal vessels has required amputation despite a functioning graft.

We feel that these initial results are encouraging. However, even if the longer term results are no better than for other synthetic or heterografts, the superior handling characteristics of the biopolymeric graft may well make this the graft of choice.

Effect of prosthetic grafts on the ipsilateral long saphenous vein

I.J. Langdon, J. Brennan, J.S. Budd and P.R F. Bell, *Leicester Royal Infirmary, Leicester, UK*

Some vascular centres, including our own, pursue a policy of preferentially using prosthetic materials for above-knee femoropopliteal bypass, saving the long saphenous vein (LSV) in case it is required for subsequent infrapopliteal bypass. The aim of this study was to determine whether the LSV is compromised by the original surgery, thus rendering it unusable if required for future use In the 10-year period 1979 to 1989, a total of 136 above-knee bypasses using either polytetrafluoroethylene or human umbilical vein grafts have been performed. Forty patients could not be further assessed due to death or major amputation. All other patients have been recalled for duplex scanning of the LSV from saphenofemoral junction to a point 10 cm below the knee. Veins with a luminal diameter of $<1{\cdot}5$ mm below the knee were considered compromised. To date 58 patients have been assessed. Forty four veins were still in good condition, 10 of which had already been used for distal bypass. One vein was found to be occluded and 3 were compromised by being narrowed. Ten patients had had unsuitable veins at the time of their original surgery. This ongoing study indicates that the LSV is rarely compromised by using prosthetic grafts for above knee femoropopliteal bypass.

Massive intestinal ischaemia: experimental pathophysiological changes leading to clinical diagnostic and management suggestions

W. Jamieson, G. DeRose and K.A. Harris, *Department of Surgery, Victoria Hospital, London, Canada*

The overall mortality rate in patients with massive intestinal ischaemia is virtually unchanged in this century. The reasons for this are· difficulty in establishing an early diagnosis at a time when bowel is salvageable and after multiple organ failure revascularization. Earlier work has shown a chemical triad of increased serum phosphate, increased white blood cell count and an increase in metabolic acidosis that aids in an early diagnosis.

Recent work in dogs with massive gut ischaemia (superior mesenteric artery ligation) has shown that cardiac and central haemodynamic changes are due to hypovolaemia and not 'septic shock' or a 'myocardial depressant factor' ($P<0{\cdot}05$) The intravascular volume is lost into the bowel (70 per cent), peritoneal cavity (22 per cent) and into all other organs and viscera 8 per cent, an indication there is a systemic vascular endothelial injury during the ischaemia interval itself. Antibiotics and fluid replacement have been shown to lengthen the reversible ischaemia time in the canine model

Early diagnosis, aggressive fluid replacement, antibiotic coverage and an awareness of the systemic microvascular injury that occurs may lower the high mortality rate in cases with massive mid-gut ischaemia.

Vascular injury and repair associated with retroperitoneal lymphadenectomy

J.L. Provan, J. Morin, M.A.S. Jewett and F M. Ameli, *The Wellesley Hospital, Toronto, Canada*

Because injury to adjacent vascular structures during retroperitoneal lymphadenectomy has the greatest potential for producing post-operative morbidity, our experience in 78 cases treated between 1976 and 1977 has been evaluated. These patients were aged 16–49 years, mean 26, and underwent retroperitoneal lymphadenectomy for non-seminoma testis tumours using an anterior transperitoneal approach carried superior to the renal hilum. Of these patients, 17 (21·8 per cent) required vascular repair. In two patients resection of the infrarenal aorta because of tumour involvement was required, and 10 patients required repair or resection of the inferior vena cava, this being repaired by lateral venorrhaphy using either vein or polytetrafluoroethylene in four patients, simple suture repair in four, and polytetrafluoroethylene tube replacement in one. Of the nine patients requiring vena caval repair, only one developed postoperative leg swelling, this being in the single patient needing tube replacement. Four renal artery injuries occurred, only one of which was repaired. Three of these four patients went on to renal artery thrombosis and subsequent nephrectomy.

Arterial and venous injury is relatively common and requires immediate repair. The results of venous repair for major caval injury are better than would be expected from review of the literature The renal arteries are particularly at risk and require appropriate and immediate repair if injured to preserve renal function.

Amelioration of micro-vascular damage in small bowel ischaemia–reperfusion injury by oxygen free-radical inhibition

G. Daly, C.A. Daly, A.L. Leahy, D. Cottell, T.F. Gorey and D.J. Bouchier-Hayes, *Beaumont Hospital, Dublin 9, Ireland*

Oxygen free-radical (OFR) activity causes damage on reperfusion after ischaemia. This was studied by quantifying microvascular damage in mid-gut ischaemia–reperfusion. OFR suppression was studied by administration of allopurinol Thirty Sprague Dawley (250 g) rats were anaesthetized with pentobartital, and randomized to receive pre-operative intraperitoneal water (group A) or allopurinol (16 mg kg^{-1}; group B). Intestinal ischaemia was induced by reversible superior mesenteric artery occlusion. In each group, villous microvascular casts were made using methylmethacrylate polymer, prior to ischaemia ($n=5$), after 10 min ischaemia ($n=5$), and after 10 min reperfusion ($n=5$). Three specimens from each animal were prepared for scanning electron microscopy (Joel 35C instrument) Microvascular appearances were compared and two factors quantified. number of complete capillary loops and arteriolar cast blebs per high power field (magnification ×650).

	Capillary loops per field			Arteriolar blebs per field		
Group	Control	Ischaemia	Ischaemia–reperfusion	Control	Ischaemia	Ischaemia reperfusion
A	28	7	5	0	11	61
B	24	24	24	0	20	60
Wilcoxon rank sum	NS	$P<0{\cdot}01$	$P<0{\cdot}01$	n s	n s	n s

Villous capillary damage occurred during ischaemia, but arteriolar disruption was paradoxically exacerbated upon reperfusion. This study supports the role of OFR in mesenteric ischaemia, points to xanthine oxidase as the source, and provides quantitative evidence of the benefit of OFR inhibition.

Dangers of large arterial damage following radiotherapy: a series of 15 cases

A.W. Halliday, P. Auckland and A.O. Mansfield, *St Mary's Hospital, London, UK*

Many years after radiotherapy treatment for malignant disease, stenosis and occlusion of large arteries may occur. Operation to restore flow is reported to be hazardous. We have reviewed a considerable experience of this unusual and difficult problem.

Between 1972–1990, fifteen patients (age 35–72 years, mean 54 years) presented with symptoms of ischaemia affecting the subclavian (7), carotid (2) and aortoiliac (6) segments. They had undergone radiotherapy 8–29 years (mean 18) earlier, for tumours affecting the breast (5), soft tissues (4), larynx/pharynx (2), cervix (2), rectum (1) and testis (1).

Fourteen required urgent treatment. Nine had a satisfactory outcome. In seven patients grafting successfully restored flow to the limb (6) and brain (1). One patient had a difficult but successful iliac endarterectomy. A patient with occlusion of the irradiated carotid artery had successful endarterectomy of the contralateral stenosed vessel. In five patients there was a poor outcome. Amputation of part or all of the upper (3) or lower (1) limb was necessary. One stump failed to heal and this patient died several months later. Another patient died after the repair of an aneurysm arising in irradiated aorta

Radiation damage to large arteries is a serious problem There is a long interval, often several decades, before symptoms occur. During that time, irradiated tissue becomes densely fibrosed, inhibiting development of collateral blood supply to ischaemic tissues. Direct approach is hazardous and can result in damage to important adjacent structures such as the ureter or brachial plexus The irradiated tissue should be avoided and flow restored by extra-anatomic bypass.

Duplex ultrasound scanning of arteriovenous fistulas for haemodialysis

J.H.M. Tordoir, *University Hospital, Maastricht, The Netherlands*

Arteriovenous (AV) fistulas constructed for vascular access have a high rate of complications Thrombotic occlusion frequently leads to loss of the access and the need for operative revision or creation of a new access In addition, infection, false aneurysms, venous hypertension and distal ischaemia, may impair the function of the AV fistula. The presence of stenotic lesions in the fistula vessels has been recognized as the major cause for the occurrence of thrombosis and haemodynamic complications. An accurate diagnosis of these stenoses is of importance for the correct treatment of complicated fistulas The value of duplex ultrasound scanning for the diagnosis of stenoses in AV fistulas, was investigated. B-mode imaging was used for recognition and subsequently doppler insonation of the fistula vessels was performed Quantitative doppler spectral analysis was correlated with the outcome of digital subtraction angiography (DSA) in 64 AV fistulas (36 Brescia–Cimino fistulas; 28 graft fistulas) in 58 patients A total number of 83 stenoses (<50 per cent diameter reduction) in 50 AV fistulas was diagnosed by DSA. The accuracy of duplex scanning in detecting these stenoses in the anastomotic vessels of brachiocephalic fistulas was 81 per cent, with a sensitivity of 79 per cent and a specificity of 84 per cent. In graft AV fistulas and in the efferent veins, better results were achieved with accuracies of 86 and 96 per cent respectively. The most accurate parameter in the doppler spectrum was the maximal systolic frequency.

It is suggested, that duplex scanning is a reliable method for the diagnoses of stenoses in AV fistulas for haemodialysis.

Cardiac risk assessment in patients with peripheral vascular disease: the limited value of the cardiac history or the ejection fraction

E.L. Rose, U. Raval, A. Lahiri, E.B. Raftery and J.D. Lewis, *Northwick Park Hospital and Clinical Research Centre, Harrow, UK*

Left ventricular ejection fracture (EF) as measured by resting radionuclide ventriculography (RNV) has become widely used as a method of pre-operative cardiac risk assessment in patients with peripheral vascuar disease (PVD). We were suspicious that EF may be normal in PVD patients with significant coronary stenoses RNV and tomographic dipyridamole thallium-201 imaging (DT1) were performed in 168 patients with PVD, 52 subsequently had coronary angiography. Only 29 per cent of the patients had coronary artery disease (CAD) on their history and resting electrocardiogram (ECG) and 12 per cent had a current history of angina, none had unstable coronary disease.

EF was abnormal (<48 per cent) in 26 per cent off the patients DT1 showed redistribution, (R) representing reversible myocardial ischaemia in 50 per cent of patients, 20 per cent only had fixed pathological perfusion defects (F) representing prior myocardial infarction and 30 per cent were normal. Positive predictive value of *R* on DT1 for significant coronary stenoses was 92 per cent. The ability of cardiac history or EF to predict DT1 results are shown below.

Cardiac history	Ejection fraction	Patients *n*	Tomographic dipyridamole thallium result		
			R (%)	F (%)	Normal (%)
Absent		111	46	17	37
Present		57	56	25	19
	Normal	124	48	15	37
	Reduced	43	53	35	12

Neither clinical history nor EF can be used to distinguish those patients with PVD who have reversible myocardial ischaemia on DT1, which we have demonstrated to have a high positive predictive value for stenoses at coronary angiography, and which is known to be associated with high peri-operative and long-term risk of cardiac events.

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BUTTERWORTH HEINEMANN

Correspondence

Unremarkable parotid tumours that prove to be malignant

Sir

The report by Nnochin *et al* (*Br J Surg* 1990; 77 917–18) is interesting and important. Unfortunately the article contains a number of errors and mis-statements about fine needle aspiration biopsy (FNAB) which reduce the value of its conclusions

1. 'Fine needle aspiration predisposes to recurrence'.

No such case has been reported using a fine needle with a single pass technique The total number of cases of local recurrence following fine needle aspiration is negligible in thousands of cases reported using this technque and any recurrences can not be attributed with any certainty to fine needle aspiration[1–9]

2. 'We find it difficult to understand how fine needle aspiration cytology can be accurate in the parotid gland . .'

We have reported as have others the extraordinary degree of accuracy in the diagnosis of salivary gland lesions, particularly pleomorphic adenoma In our experience the distinction can be made in every case between benign lesions and pleomorphic adenoma[1–3,8–14]. Differences in accuracy may be partly explained by variations in aspiration technique[15].

3. 'Proponents of fine needle aspiration .. may be right but so far they have not published data that demonstrate how useful the technique is in decision making'

We and others have published and cited other data which clearly shows how the accurate preoperative diagnosis influences management[9–14,16]. In the cases of adenolymphoma local excision is all that is necessary, in the case of tuberculous lymphadenitis and secondary carcinoma an operation may not be necessary[10,13,17]

4 The authors pose the question whether formal parotidectomy constitutes 'therapeutic overkill' for benign lesions and conclude that their results support the case that it does not

Our unequivocal answer is that it is overkill. Moreover it will cause considerable unnecessary morbidity. We recently underlined this very point by documenting the significant complications of formal parotidectomy in our moderately experienced hands[18] It is likely that a highly experienced group such as Hobsley's will have a lower serious morbidity rate; the fact is that most parotid surgery is performed in district general hospitals by competent surgeons who irregularly see a small number of parotid lesions. In these hands the complications are bound to be higher and an accurate preoperative diagnostic test such as fine needle aspiration should be encouraged provided local cytologic skills are available despite the very rare possibility of late recurrence following needle puncture

The authors imply in their discussion that because a preoperative diagnosis is obtained that the subsequent surgical treatment may be inadequate. This can not be a reason to avoid FNAB In fact we advocate a similar procedure to theirs for pleomorphic adenoma Their argument is not logical and their excellent results in the 20 cases of malignancy cannot be attributed to the avoidance of FNAB. It is likely that most if not all of these lesions would have been diagnosed by FNAB as would all of the pleomorphic adenomas and the surgeon would thus have been prepared to perform an operation of the required radicality More importantly, how many of the 539 patients underwent surgery more radical than was necessary to deal with the pathology? The data presented is insufficient to calculate this

E. R. T. C. Owen
A. E. Kark*

Departments of Surgery
Hammersmith Hospital RPMS
London W12 0HS
*and *Clementine Churchill Hospital*
Harrow on the Hill
UK

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Authors' reply

Sir

Thank you for the opportunity to comment on the letter from Owen and Kark.

1. The words, 'Theoretically, preliminary biopsy of these lumps even by', at the beginning of the sentence have been left out of the quotation It will be many (approximately 20) years before the risk of recurrence is accurately known.

2. Accuracy of cytology is reported from centres with special expertise It could be that district hospitals need to make a choice between expert paratodectomists and expert cytologists and we would not like to forecast the outcome of analysis of this problem from the economic standpoint. The occasional parotidectomist perforce supplies only occasional material for his cytologist The last four occasions on which we have been provided with a prior cytological diagnosis of a lump from other centres yielded the following comparisons with the post-parotidectomy diagnoses:

Cytology	Histology
Pleomorphic adenoma	Chrondrosarcoma
Schwannoma	Monomorphic adenoma
Papilloma	Pleomorphic adenoma
Lymphoid sialoadenitis	Adenoid cystic carcinoma

3 and 4. We reiterate the finding in our paper that FNAB would have altered our management in only 0 185 per cent of cases.

G. T. Watkin
M. Hobsley

Department of Surgery
The Rayne Institute
London WC1E 6JJ
UK

Epidural analgesia in colonic surgery

Sir

We have read with great interest and concern the article by Bredtmann *et al.* (*Br J Surg* 1990; 77· 638–42) In this study the authors have attempted to validate their hypothesis that colonic surgery patients benefit from continuous thoracic epidural anaesthesia (TEA).

We would like to raise the following points particularly with regard to the practical conduct of the two analgesic systems used in the study which in our opinion rendered the interpretation of the data invalid.

Firstly the authors state that the mean number of blocked dermatomes in group 1 (TEA) was 8 3 on the first day with increasing bupivacaine requirements despite a receding block. In the next sentence they state that the number of patients receiving bupivacaine fell from 55 on the first day to 34 Thus 21 patients in the group receiving TEA did not in fact receive this during their study period. Indeed they go on to show in *Figure 3* that throughout the study period both groups received systemic analgesia and even more surprisingly the number of patients receiving systemic analgesia never exceeded 39 (out of 59) in group 2. This group also was being inadequately treated *vis-à-vis* analgesia.

Secondly the authors show that 60 patients had preoperative 'lung disease' By itself this classification is insufficient. When combined with the indiscriminate use of postoperative mechanical ventilation in 54 patients without explanation, this makes interpretation of all morbidity data difficult.

In summary we conclude from this study that the authors' failure to show any clear benefit on their observed parameters may be a consequence of comparison between one inadequately controlled analgesic regime (TEA) over another equally inadequate regime (GA plus opiate) resulting in considerable overlap between the two groups We are aware of data from two other studies[1,2] which also failed to show any advantageous effects of postoperative epidural analgesia following abdominal surgery but again the patients did not receive optimal analgesia in these studies.

Future studies comparing the analgesic effects of two such different techniques must endeavour to provide and demonstrate analgesia in both groups in order to elucidate a potential advantageous effect of one over the other.

N. B. Scott
H. Kehlet

Department of Surgical Gastroenterology
Hvidovre Hospital
2650 Copenhagen
Denmark

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Authors' reply

Sir

We agree with Dr Scott and Dr Kehlet that the quality of analgesia was not optimal However, realistic clinical studies differ from experimental designs in that factors distracting from the study are not eliminated We did not exclude those patients in whom epidural anaesthesia was associated with technical deficiencies

One of the shortcomings of the study was that not all group I patients received their bupivacaine doses at every measuring point and that systemic analgesics were required by some patients. However, all group I patients had sufficient segmental analgesia at the end of surgery and all of them received bupivacaine in the postoperative period. Analgesia in group I was comparably better than the control group considering lower requirements of systemic analgesics and lower pain scores in this group.

Pre-existing cases of lung disease were either emphysema and/or chronic bronchitis, the incidence being equal in both groups. The high rate of postoperative mechanical ventilation reflects standard of care at our hospital. Standard of care does not necessarily mean that other institutions should follow the same concept, but reflects the conditions of postoperative care at our institution. In both groups the rate of postoperative mechanical ventilation was similar which correlates to the equal distribution of pre- and intraoperative pulmonary risk factors. Our results on pulmonary complications are going to be published[1].

The authors compare our paper to two publications by Seeling *et al* and by Hjortso *et al.* One essential difference in the study design is that both Seeling and Hjortso combined local anaesthetic agents with opiates Both studies failed to show that this regimen provided optimal analgesia We studied the clinical application of epidural analgesia, including factors like technical difficulties and practicability under the conditions of our hospital. Yet, our results are similar to the above.

R. D. Bredtmann

Department of Anesthesiology
Altona General Hospital
Paul-Ehrlich-Str 1
D-2000 Hamburg 50
Germany

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Experimental study of starch-induced intraperitoneal adhesions

Sir

McEntee and colleagues (*Br J Surg* 1990, 77: 1113–14) report a most interesting series of experiments. It is difficult to escape their conclusion that starched gloves should be avoided However, their findings raise a further intriguing question, namely the role of the gloves themselves, since in their study 37 per cent of rats developed adhesions after simple starch-free glove laparotomy. Perhaps hypersensitivity to glove chemicals and even to new glove coatings plays a part

It has occurred to us that such a reaction might explain three cases of postlaparotomy adhesive obstruction which recently taxed our unit. All required re-exploration only to find panperitoneal obliterating and inseparable adhesions, with tissue friability rendering adhesiolysis impossible Starch-free gloves had been used

C. A. Eynon
W. H. F. Thomson

Gloucester Royal Hospital
Gloucester GL1 3NN
UK

Aetiology of pancreatic cancer

Sir

In the excellent review by Haddock and Carter (*Br J Surg* 1990; 77 1159–66) they highlighted some of the familial cases. There is evidence for an increased incidence of pancreatic carcinoma in the two autosomal dominant familial polyposis conditions namely familial polyposis coli[1] and Peutz-Jeghers syndrome[2] A study of oncogenic expressions in these familial cases may help us to understand the pathogenesis of pancreatic carcinoma as has been shown by our understanding of colonic carcinoma that is beginning to emerge by studying cases of familial polyposis coli[3].

K. C. Saw

Department of Urology
Addenbrooke's Hospital
Cambridge CB2 2QQ
UK

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Treatment for paraphimosis

Sir

The puncture technique described by Hamdy and Hastie (*Br J Surg* 1990; 77: 1186) is indeed an effective means of reducing oedema, hence facilitating manipulative reduction of a paraphimosis. The authors prefer this to hyaluronidase injection. In fact the two techniques are most effective when used together. A 21G needle, on a 1 ml syringe containing hyaluronidase, is used to make multiple punctures in the oedematous foreskin, as the authors describe, but at each puncture a small amount of hyaluronidase (about 0.05 ml) is injected. This diffuses through the flimsy oedematous connective tissue, liquifying it and allowing it to spray out through the multiple puncture sites on gentle compression. The result is complete collapse of the oedematous foreskin within a few seconds. The procedure is painless.

I first saw this technique in rural South Africa where patients frequently presented several days after onset when, despite the extensive oedema, the glans was never ischaemic. It is, therefore, hardly the surgical emergency the authors describe, but nonetheless is amenable to reduction in the accident and emergency department. The authors seem to imply that anaesthesia was not necessary for the manipulative reduction. In my experience, this awkward condition induces considerable patient anxiety and reduction is facilitated by a lignocaine penile block. This will also allow division of the constriction ring, which occasionally is necessary to achieve reduction in more chronic cases.

R. J. Baigrie

Department of Surgery
John Radcliffe Hospital
Oxford OX3 9DU
UK

Gallstone ileus

Sir

I enjoyed the review by Clavien and colleagues (*Br J Surg* 1990; 77: 737–42). One point, however, requires more emphasis. Although gallstone ileus is an uncommon cause of mechanical small bowel obstruction (1.7 per cent in their series) it is a frequent cause of obstruction in elderly patients without irreducible hernias or scars of previous laparotomy.

In Fremantle Hospital, Western Australia, gallstone ileus was the cause of small bowel obstruction in 9 (21 per cent) of 42 patients admitted over a 10-year period (1980–1989 inclusive) who were over the age of 65 years and who had no external hernias or scars of previous abdominal surgery. Indeed, of the total of 11 patients with gallstone ileus admitted over this period, only two had abdominal scars and none had external hernias. At Fremantle Hospital, early laparotomy is advocated for patients with mechanical small bowel obstruction which cannot be attributed to adhesions or hernias. After careful resuscitation of these patients (fluid replacement, correction of plasma electrolyte disturbances and treatment of intercurrent illnesses), further investigation is not thought necessary.

Clavien and colleagues do not comment on the presence of abdominal scars or hernias in the patients of their series. I wonder how ultrasonography, gastrointestinal contrast studies and computed tomography help in the management of the selected group I have described.

H. Gajraj

University Department of Surgery
Fremantle Hospital
Fremantle
Western Australia

Authors' reply

Sir

We thank H. Gajraj for the interest shown in our paper. There is little doubt that in the absence of previous abdominal surgery or an incarcerated hernia, gallstone ileus should be strongly considered as a cause of mechanical bowel obstruction in the elderly. The incidence of 21 per cent in this group does not appear to be excessive. The major cause of mechanical bowel obstruction is neoplasm, although adhesions unrelated to previous surgery is not exceptional. On the other hand, the presence of abdominal scars should not rule out the possibility of gallstone ileus. Indeed adhesions may cause the impaction of a stone that otherwise might pass spontaneously. In our series, ten out of 37 patients with gallstone ileus had had previous abdominal surgery. Even in the absence of abdominal scars other diagnoses remain more common, therefore full preoperative diagnostic investigation is justified. In the situation where the plain abdominal radiograph is highly suggestive of gallstone ileus (46 per cent in our series) ultrasonography is still warranted for the identification of residual cholelithiasis or choledocholithiasis.

P.-A. Clavien
J. Richon
S. Burgan
A. Rohner

Department of Surgery
Clinic of Digestive Surgery
University Hospital
1211-Geneva-4,
Switzerland

Management of the Mirizzi syndrome and the surgical implications of cholecystcholedochal fistula

Sir

Messrs Bauer *et al* deserve to be complimented on their informative contribution dealing with the classification and surgical management of the Mirizzi syndrome (*Br J Surg* 1990; 77: 743–5). We agree with the authors that confirmation of preoperative diagnosis by ERCP (endoscopic retrograde cholangiopancreatography) is important but would like to draw attention to the additional advantages of a nasobiliary drain, inserted at ERCP for those with a type II Mirizzi syndrome. After the diagnostic cholangiogram had identified the stone protruding into the common hepatic duct through the choledochal fistula, a nasobiliary drain is manipulated so that its tip is above the obstructing stone. The nasobiliary drain allows drainage of the intrahepatic ducts, avoiding the risks of septic cholangitis[1,2]. During surgery, the nasobiliary drain is easily palpable and aids the identification of the common bile duct in a severely inflamed and fibrosed Calot's triangle. Like Bauer *et al* we incise the gallbladder directly over the stone. After stone extraction, the nasobiliary drain is then visible in bile duct. We believe that cholecystcholedochoduodenostomy is unnecessary provided a careful partial cholecystectomy is done taking care to leave enough of a cuff to allow closure around a T tube.

G. Dewar
S. C. S. Chung
A. K. C. Li

Department of Surgery
Prince of Wales Hospital
Shatin, NT
Hong Kong

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Effect of surgery on the systemic inflammatory response to intermittent claudication

Sir

We were interested to read the paper by Hickey *et al* (*Br J Surg* 1990; 77: 1121–4) but have some reservations about the methodology used to obtain the data.

Hickey *et al.* make the point that the systemic effects of ischaemia are mediated through neutrophils that have been activated in the ischaemic limb. The authors reach their conclusions from data suggesting that the neutrophil activation occurs during intermittent claudication. This is based on demonstrating increased difficulty in filtration of neutrophils. There is a substantial literature on the effects of purification techniques and activation of white blood cells[1]. It has been shown that the temperature at which the blood is stored, sedimentation and centrifugation can drastically alter the expression of molecules representing white blood cell 'activation' and therefore their filterability. In their assessment of neutrophil filterability, other than 'a pellet of granulocytes (97% neutrophils) was separated from heparinized whole blood by gradient density centrifugation' the authors have not made clear their particular method of purification There is no method of purifying neutrophils that does not involve the techniques of sedimentation or centrifugation. The trypan blue exclusion test will not address this aspect of neutrophil function This has important implications for the interpretation of that section of data The neutrophil filtration data in this study may owe more to the method of preparation of these cells than to *in vivo* white cell activation

Atherosclerosis is a generalized disease and the presence of vascular renal pathology is supported by their findings of an increased resting albumin.creatinine ratio (ACR) in claudicants as compared to controls as does the good correlation between pressure recovery time (PRT) and percentage change in ACR in claudicants. The wide range of ACRs observed makes the relatively small changes following exercise of doubtful significance. Explanations other than that proffered may be more appropriate.

The authors have elected to use the mean value to describe sets of data Since much of the data does not have a Gaussian distribution this is probably not appropriate. In particular, the use of changes in the mean of the ACR data of claudicants has resulted in a much larger shift in ACR being represented (167 per cent increase) than is actually the case In applying tests of significance the authors seem to have accepted this point by using non-parametric tests. They indicate that differences between the groups were tested for significance by the Wilcoxon signed rank test. Whilst this is suitable for paired data, differences between groups (controls to claudicants) would best have been assessed using a test for unpaired data The Mann–Whitney or Wilcoxon rank sum test would have been appropriate.

In conclusion, whilst it is attractive to think of the calf as a source of activated white blood cells in claudicants, the data presented in this paper do not support this point of view. In fact, such is the affinity of activated white blood cells for endothelium, it is most unlikely that they would escape from the calf and certainly would be trapped in the pulmonary circulation.

We congratulate the authors on their imagination but cannot agree with their conclusions

S. Sarin
P. D. Coleridge Smith
J. H. Scurr

Department of Surgery
The Middlesex Hospital
London W1N 8AA
UK

1 Douglas TF, Collins L. Increased expression of C3b receptors on polymorphonuclear leukocytes induced by chemotactic factors and by purification procedures. *J Immun* 1983, **170**: 370–5

Authors' reply

Sir

We expected a degree of sceptisism at the novel idea that claudication could incite a systemic response, but feel that the points made by Sarin *et al.* are unsubstantiated.

Filterability of neutrophils is an accepted method of assessing their activation and our technique has been carefully developed by an experienced haemorheologist (S.B.) We felt it inappropriate to publish details in a surgical paper, but they are available on request. We appreciate that any *in vitro* analysis may be fraught with problems, but these were minimized by taking serial samples from each patient through an identical purification regimen, which produced reproducible results. All analyses were performed 'blindly', at a constant temperature and were completed within 4 hours of venepuncture. It would seem unlikely then, that the consistent decrease in neutrophil filterability which was observed after exercise in all claudicants, but not after surgery or in controls, was due to errors in cell preparation The trypan blue exclusion test is the usual method of assessing leukocyte viability after separation for filterability experiments[1] and we did not claim that it provided any information regarding function

Postexercise increases in ACR are unlikely to be due to the properties of atherosclerotic renal vessels The increases are transient, reversed by bypass surgery and are similar to those seen in response to other inflammatory stimuli such as pancreatitis, burns and trauma, where atherosclerosis is absent[2,3] Although there was a wide range of ACRs observed, the postexercise percentage changes were not small. perhaps Sarin *et al.* failed to notice the logarithmic scale of *Figure 2*

To avoid relying entirely on statistical evidence to communicate our findings, the raw data from each patient were clearly displayed graphically for the reader to examine. In addition, the appropriate analysis for paired data (Wilcoxon signed rank) was performed, with the results added above each figure.

Our paper did not actually address the question of whether neutrophil activation occurred in the limb itself, or systemically by inflammatory mediators (e g thromboxane A_2) released from the ischaemic muscle during reperfusion. However, Sarin *et al* cite no evidence to support their claim that activated white cells would not escape from the calf, or be trapped in the lung, indeed increased numbers of activated neutrophils have been demonstrated by others in the venous blood of patients with critical lower limb ischaemia[1] and claudicants[4].

Sarin *et al* have, however, highlighted the difficulty of studying neutrophil activation, endothelial damage and vascular permeability by *in vitro* methods in human subjects. We have, therefore, continued our investigations using direct techniques using an *in vivo* model and hope to publish the results soon

We are keen to discuss explanations of our preliminary findings, but feel that Sarin *et al.* have failed to produce a more plausible or imaginative alternative to our own conclusion

N. C. Hickey
P. Gosling
S. Baar
C. P. Shearman
M. H. Simms

Department of Surgery
Selly Oak Hospital
Birmingham B29 6JD
UK

1. Nash GB, Thomas PRS, Dormandy JA. Abnormal flow properties of white blood cells in patients with severe ischaemia of the leg. *Br Med J* 1988; **296**: 169–91
2. Shearman CP, Gosling P, Walker KJ Is low level proteinuria a predictor of severity of acute pancreatitis? *J Clin Path* 1989; **42**: 1132–5
3. Gosling P, Sutcliffe AJ, Cooper MA, Jones AF. Burn and trauma associated proteinuria: the role of lipid peroxidation, renin and myoglobin *Ann Clin Biochem* 1988; **25**: 53–9
4. Neumann FJ, Waas W, Diehm C *et al* Activation and decreased deformability of neutrophils due to intermittent claudication *Clin Haemorheology* 1989; **9**: 505.

Book reviews

Techniques in Arterial Surgery

J J Bergan and J. S T. Yao, eds 220 × 284 mm Illustrated 1990. London· Saunders. £78.50 hardback.

Surgeons will always be interested in improving their operative techniques. This is particularly true in a field such as vascular surgery where, as the editors, John Bergan and James Yao state in their preface, there have been many refinements over the past decade as well as the introduction of a whole new battery of minimally invasive procedures. I do not think that there is any doubt that vascular surgeons today require to be considerably more versatile in thought and deed and more open minded to the variety of therapeutic options available than was the case 10 or 15 years ago. In addition to the wide coverage of every area of arterial reconstruction there are sections on balloon angioplasty, laser angioplasty, atherectomy, angioscopy and inferior vena cava filter placement. Some vascular textbooks are academically and pictorially impressive but of little practical assistance when it comes to dealing with a difficult case Not so this book. The text is full of the sort of practical detail that makes all the difference in difficult technical situations. It is well illustrated. In short this is the best book on techniques in vascular surgery that I have yet come across It can be wholeheartedly recommended.

C. Jamieson

Consultant Surgeon
St Thomas' Hospital
London SE1 7EH
UK

Laparoscopy for Surgeons

B. A. Salky. Pp. 168 Illustrated. 1990, Igaku-Shoin, New York £85.00.

The current interest in surgical laparoscopy will undoubtedly lead to a plethora of books on the subject and the author must be congratulated on his speed off the mark This book has been written as an 'atlas' with the aim of demonstrating the use of laparoscopy to surgeons who may not be aware of its potential, both diagnostic and therapeutic. The chapters have been neatly divided into instrumentation and technique, abdominal pain, abdominal masses, liver disease, ascites, therapeutic procedures and trauma. All except the first and last are made up entirely of case presentations illustrated in each case with excellent colour plates of the laparoscopic views described. The chapters on liver disease and ascites are particularly well illustrated and suggest that laparoscopy is a much underused tool in the investigation of these patients. As surgical units develop the therapeutic side of laparoscopy and surgeons become aware of the excellent views permitted by current instrumentation, they will undoubtedly explore the potential of laparoscopy in other fields. As a guide for this purpose *Laparoscopy for Surgeons* is ideally suited; however at the price of £85 it will probably prove too expensive

S. Paterson-Brown

Department of Surgery
The Royal Infirmary
Edinburgh EH3 9YW
UK

Essential Surgery: Problems, Diagnoses and Treatments

H. G. Burkitt, C R G. Quick and D. T Gatt. Pp. 800. Illustrated. 1990, Edinburgh Churchill Livingstone. £24 95

Not the least interesting feature of this book is the circumstances of its authorship, in that only one of the three authors was a consultant surgeon when the book was being written, while the other two were junior hospital doctors. Moreover, two of the authors were originally dentists and one of these is now a general practitioner rather than a consultant surgeon. The stated aims of the book are to cover general surgery and urology to a level suitable not only for undergraduate medical students but also for junior hospital doctors up to the level of surgical senior house officer, for general practitioners and as a reference text for doctors in specialties other than surgery. The book adopts a problem-solving rather than a disease-orientated approach to diagnosis and treatment, or at least it makes that claim. However, the titles of the chapters rather belie that claim in that they include chapter headings such as Pancreatitis and Appendicitis, and Peptic Ulceration and Related Disorders. Nevertheless, it is noteworthy that the contents are divided into four parts – basic surgical principles, principles of accident surgery, symptoms, diagnosis and management; and finally management problems of surgical inpatients. This arrangement allows the scene to be set via surgical physiology and the principles of surgical investigation, operation and cancer management for the later more detailed consideration of surgical topics. One of the best parts of the book is the final part on the management of surgical inpatients· there are chapters on medical problems in surgical patients, complications, preoperative management, postoperative management and fluid balance and nutrition. The book is full of sound sense and the views it expresses are clear cut and conventionally wise. There is a very real appreciation of the needs of students, for example, this extends to starting the chapter on the principles of operative surgery by defining such terms as 'otomy', 'ostomy', 'ectomy'. The print is clear and the illustrations are good photographs or excellent descriptive diagrams. The format is of a soft-covered book which is attractively presented in red and black, and I believe it will prove popular with the audience for whom it was intended.

M. Hobsley

Department of Surgery
University College and Middlesex School of Medicine
London W1N 8AA
UK

Atlas of Surgery of the Liver, Pancreas and Biliary Tract

K. W. Warren, R. L Jenkins and G D Steele Jr , eds. 305 × 260 mm. Illustrated. 1990 New York Appleton and Lange. £88.

The editors describe a number of common and uncommon hepatobiliary operations which they recommend as currently acceptable procedures. Despite the undoubted experience of the senior author and his colleagues, many of the operations described appear to be of historical interest only Although the editors could be excused for not including recent innovations such as laparoscopic cholecystectomy, there are notable omissions. For example, no mention is made of segment III cholangiojejunostomy, an operation now well established in the palliation of cholangiocarcinoma.

In the section on Bile Duct Injury, the senior author describes his own mucosal graft technique, a left duct approach (incorrectly named intrahepatic hepaticojejunostomy) and the Longmire procedure. Illustrations accompanying the latter operation incorrectly show the left hepatic duct traversing the substance of the left lobe of the liver, being one of a number of errors present in often over-simplified diagrams. Over fifteen operations for the treatment of acute and chronic pancreatitis are described in the section on Pancreatic Surgery. Whilst the training surgeon might be tempted to try his hand at one of these elegantly conceived procedures, he or she might not be reassured of their indication by the authors' statement that 'the pathological manifestations of chronic pancreatitis are so variable that special situations demand individualization in the choice of the operation'

The authors have opted to use the more confusing American terminology in describing hepatic resections. A number of anatomical classifications of the liver are illustrated but there is no description of segmental resection. The *Atlas* describes both hepatic and pancreatic transplantation, a variety of portal–systemic shunts and concludes with two sections on radiological and endoscopic procedures. The latter contribution from Dr David Carr-Locke is well presented and illustrated but the inclusion of these alternative treatments for pancreatic and biliary disease only serve to further confuse the reader, who is unable to establish the current accepted practice of the editors.

In the preface, the authors have indicated that 'the accepted becomes provincial ... as knowledge expands and concepts change' In this text they have given the impression that hepatobiliary and pancreatic surgery has stood still on the other side of the Atlantic. Rather grudging reference is made to the major contribution to the specialty by French surgeons but Claude Couinaud would be pleased to have his own work recognized by his American colleagues who have given him the middle name of 'LeFoie'. I suspect that this *Atlas* will, in its present form, have considerable difficulty in competing with already established texts

O. J. Garden

Department of Surgery
The Royal Infirmary
Edinburgh EH3 9YW
UK

Notices and announcements

22–25 April 1991
4th International Symposium on Cardiovascular Pharmacotherapy
Geneva, Switzerland
Information ISCP'91, c/o AKM Congress Service, PO Box CH-4005, Basel, Switzerland

3 May 1991
Somatostatin '91 and Other Peptide Analogues
Leicester, UK
Information Mr P. K. Donnelly, Department of Surgery, Leicester General Hospital, Gwendolen Road, Leicester LE 5 4PW, UK

4–5 May 1991
5th International Meeting of the Australian and New Zealand Society of Phlebology
Sydney, Australia
Information Dr G Mark Malouf, Secretary, ANZ Society of Phlebology, PO Box 2166, North Parramatta 2151, Sydney, Australia

8–10 May 1991
Blood Vessel Imaging Using Ultrasound Techniques
Torquay, UK
Information. Mr K N Humphries, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK

8–11 May 1991
Melanoma '91, Brighton International Melanoma Conference
Brighton, UK
Information Dr N Kirkham, Department of Histopathology, Royal Sussex County Hospital, Brighton BN2 5BE, UK

8–11 May 1991
XXVIth Congress of the European Society for Surgical Research and the VIIIth Tripartate Meeting of The Surgical Research Society and The Society of University Surgeons
Salzburg, Austria
Information ESSR Congress Office, 1st Surgical Department, Landeskrankenanstalten, Mullner Hauptstrasse 48, A-5020 Salzburg, Austria

15–18 May 1991
Annual Meeting of the American Association for Cancer Research
Houston, Texas, USA
Information American Association for Cancer Research, Public Ledger Building, Suite 816, Sixth and Chestnut Streets, Philadelphia, PA 19106, USA

17 May 1991
British Association for Endocrine Surgeons
Cambridge, UK
Information Mr A W. Goode, Surgical Unit, 4th Floor Alex Wing, The Royal London, London E1 1BB, UK

20–22 May 1991
Trauma 91
Witwatersrand, South Africa
Information Gwen Watkins, Kennedy, Watkins & Associates, 27 Landau Terrace, Richmond 2092, South Africa

20–24 May 1991
Pacific Association of Paediatric Surgeons 24th Annual Meeting
Hong Kong
Information Secretariat, PAPS Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

24–25 May 1991
Surgical Infection Society – Europe, 4th Annual Meeting
Athens, Greece
Information: Triaena Congress, 22–24 Harilaou Trikoupi Street, GR-106 79 Athens, Greece

24–25 May 1991
MedTech '91
Trondheim, Norway
Information: Laser-Medizin-Zentrum GmbH, Koordinations Buro MedTech, Krahmerstr. 6–10, 1000 Berlin 45, Germany

30 May–1 June 1991
4th International Symposium on the Biology, Immunology and Surgery of the Greater Omentum
The Netherlands
Information Secretariat, 4th International Omentum Symposium, Mrs W. J Buys-Utrecht Cancer Research Centre, Servaasbolwerk 14, 3512 NK Utrecht, The Netherlands

June 1991
33rd Annual Meeting of the International College of Angiology
Singapore
Information International College of Angiology, 1044 Northern Blvd, Ste 103, Roslyn, New York 11576, USA

2–14 June 1991
Methods of Immunologic Research and Diagnosis
Buffalo, New York, USA
Information: James F Mohn, Director, The Ernest Witebsky Center for Immunology, 272 Sherman Hall, Buffalo, New York 14214, USA

6–8 June 1991
5th European Congress of the Society for Surgery of the Shoulder and the Elbow
Wurzburg, FRG
Information Prof. Dr. med. J Eulert, Orthpadische Universitatsklinik, Konig-Ludwig-Haus, Brettreichstr 11, 8700 Wursburg, FRG

9–12 June 1991
Fifth International Conference on Malignant Lymphoma
Lugano, Switzerland
Information: F. Cavalli, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

11–13 July 1991
XVIth International Update on Liver Disease
London, UK
Information Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

12–13 July 1991
Hong Kong Surgical Forum
Hong Kong
Information Vera Fung, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

14–16 July 1991
Techniques in Pulmonary and Oesophageal Surgery
Liverpool, UK
Information Mr R J. Donnell, Cardiothoracic Centre, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB, UK

25–31 August 1991
International Surgical Week
Stockholm, Sweden
Information: Scientific Secretariat, 155, Hauptstrasse 63, PO Box 411, CH-4153, Reinach BL1, Switzerland

1–6 September 1991
6th World Congress in Ultrasound
Copenhagen, Denmark
Information Spadville Congress Service, Sommervaj 3, DK-3100 Hornbaek, Denmark

4–6 September 1991
1st European Conference on Advances in Wound Management
Cardiff, UK
Information. Christine Jones, Macmillan Conferences, 4 Little Essex Street, London WC2R 3LF, UK

7–10 October 1991
5th Congress of the European Society for Organ Transplantation
Maastricht, The Netherlands
Information 5th ESOT Congress, Conference Agency Limburg, University Hospital Limburg, PO Box 1918, 6201 BX Maastricht, The Netherlands

7–9 November 1991
3rd Combined Meeting of the Nederlandse Vereniging voor Thoraxchirurgie and the Deutsche Gesellschaft für Thorax-, Herz- und Gefässchirurgie
Maastricht, The Netherlands
Information Organizing Secretariat, Conference Agency Limburg, University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

17–23 November 1991
Surgery of the Pancreas, Liver and Biliary System
Edinburgh, UK
Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

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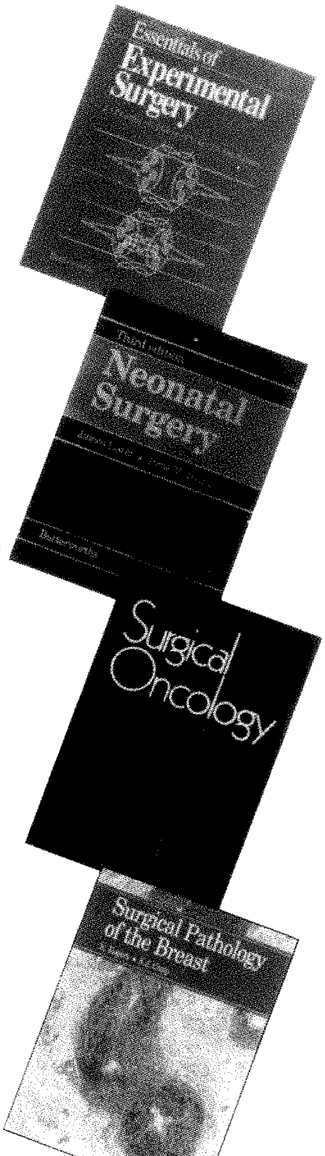
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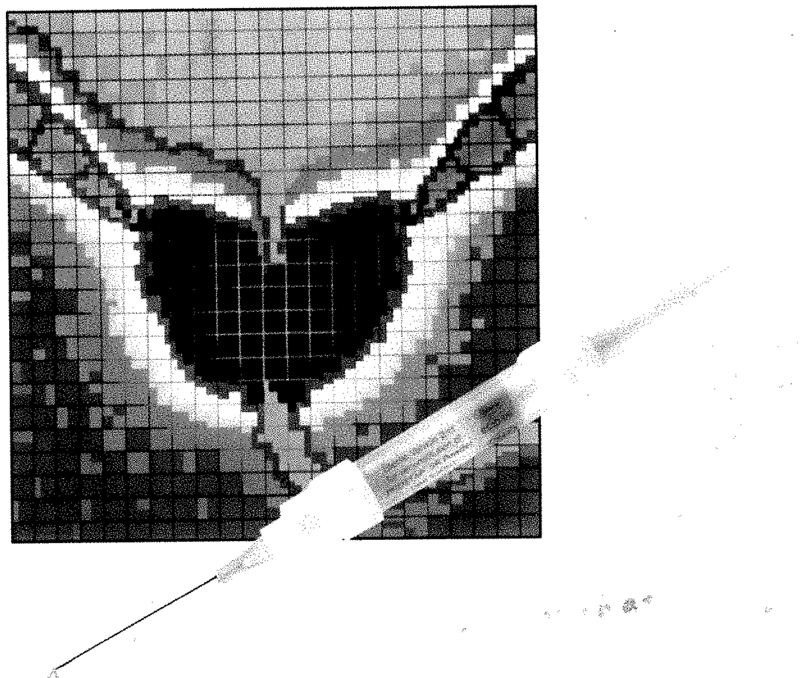

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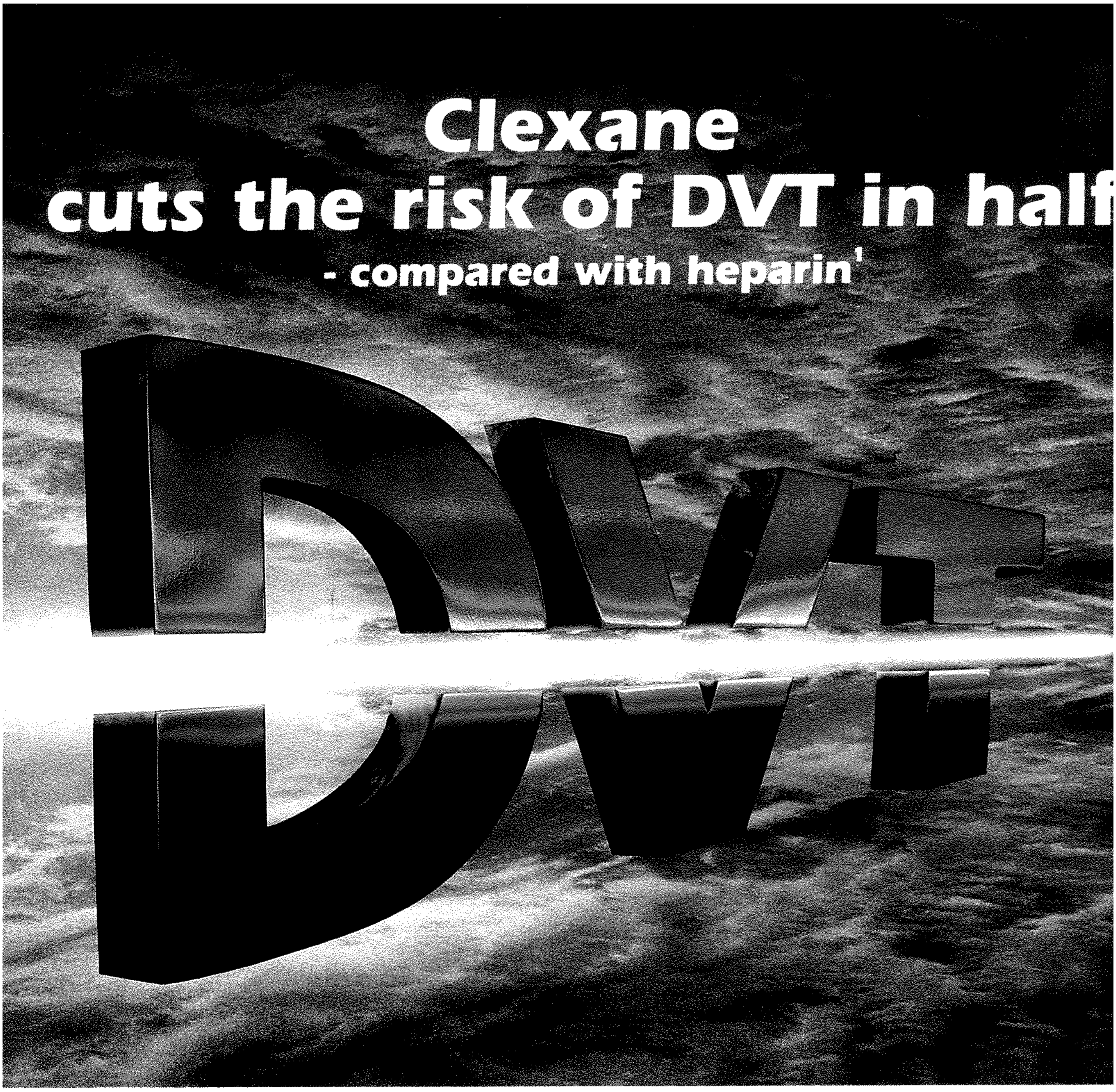

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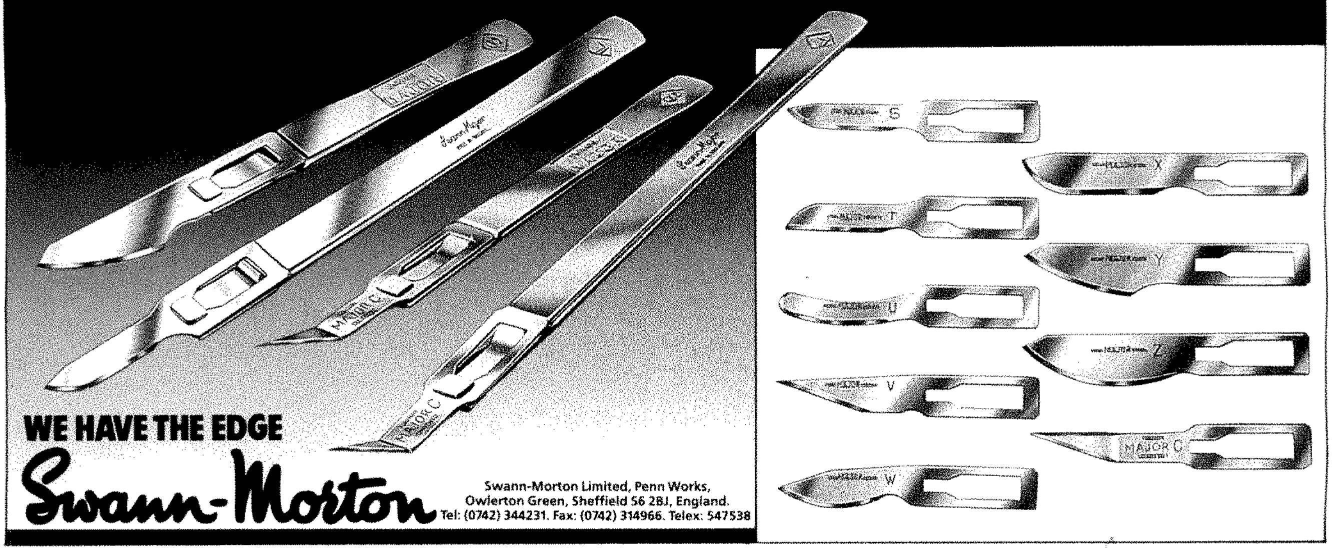

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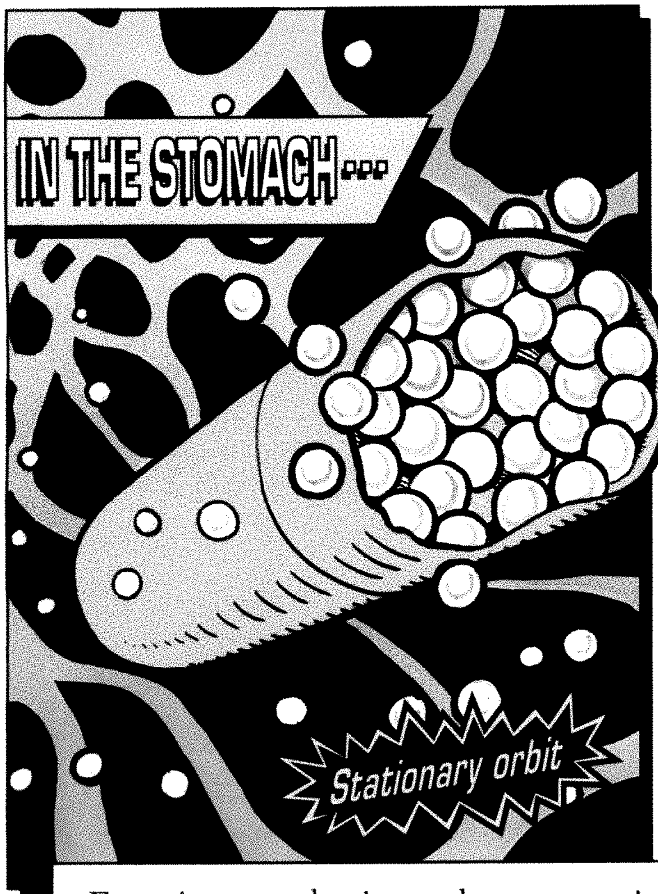

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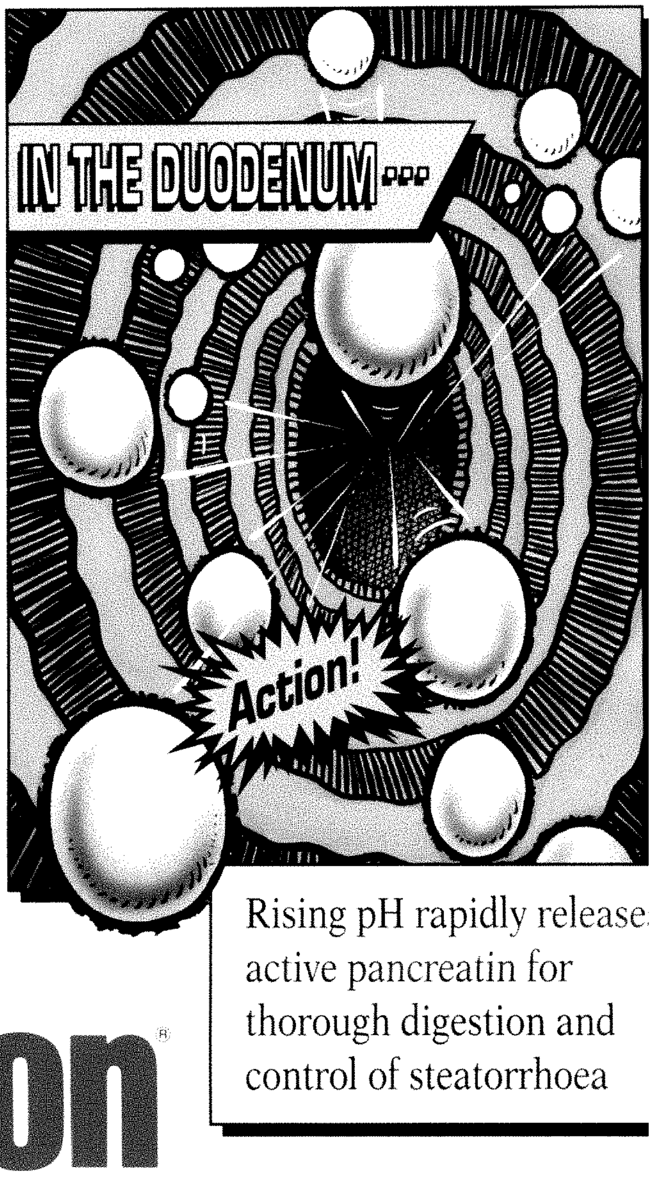
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Laparoscopic cholecystectomy and the common bile duct

The past twelve months has seen a remarkable change in the management of symptomatic gallstones. In many centres laparoscopic cholecystectomy has superceded oral and percutaneous dissolution therapies, extracorporeal shock wave lithotripsy and standard and mini-laparotomy cholecystectomy as the procedure of choice for symptomatic gallbladder stones[1–3]. In comparison with standard cholecystectomy, the laparoscopic approach appears to be associated with minimal morbidity, shorter hospital stay, earlier return to working fitness and better cosmetic result[4].

Common bile duct stones are known to occur in as many as 15 per cent of all patients undergoing standard cholecystectomy[5]. The advent of laparoscopic cholecystectomy has challenged traditional teaching on the timing, method of investigation and management of common bile duct stones and currently there are no guidelines as to the best approach to this problem. Common bile duct stones have been removed endoscopically at laparoscopy via the cystic duct or by laparoscopic choledochotomy (Reddick EJ, personal communication, 1990). However, the efficacy of this approach will need evaluation and the technology required is still in the early stages of evolution. It is important, therefore, that surgeons undertaking laparoscopic cholecystectomy develop algorithms for the management of patients with common bile duct stones.

Two approaches are possible for the patient who presents with jaundice. Firstly, a standard laparotomy cholecystectomy with exploration of the common bile duct or, secondly, retrograde endoscopic removal of the common duct stone before laparoscopic cholecystectomy. The retrograde endoscopic approach to common bile duct stones is now the preferred option in unfit, elderly, patients, many of whom do not subsequently require cholecystectomy[6]. In young patients, however, laparotomy and exploration of the common bile duct should be considered the treatment of choice since the morbidity of the procedure is low[7] and the long term effects of endoscopic sphincterotomy remain unknown.

Investigations for co-existent common bile duct calculi in patients undergoing laparoscopic cholecystectomy may be performed preoperatively or peroperatively Preoperative ultrasonography is the most appropriate investigation for suspected gallbladder stones[8] but is unreliable for detecting stones in the common bile duct. Alternative preoperative options include intravenous cholangiography (IVC) and endoscopic retrograde cholangiography (ERC). In the past, serious allergic reactions to the iodine based contrast medium and suboptimal visualization of the biliary tree led to the abandoning of IVC as a method for detecting common bile duct stones. Recent modification of the contrast medium has significantly reduced the risk of allergic reaction, while advanced tomography has reduced the number of suboptimal examinations. Thus, IVC is theoretically an attractive method for screening the extrahepatic biliary tree. However, its exact role will have to await further clinical evaluation.

ERC is not a practical method of screening for common bile duct stones. It is relatively invasive, requires intravenous sedation and is associated with a risk of sepsis and pancreatitis[9]. However, ERC should be considered as a primary investigation in patients with historical, clinical or biochemical evidence of choledocholithiasis. If common bile duct stones are detected preoperatively, endoscopic sphincterotomy may be performed in the elderly patient before laparoscopic cholecystectomy, but it may be that younger patients will be better served by laparotomy and exploration of the common bile duct with preservation of the choledochoduodenal sphincter.

The alternative approach to silent common bile duct stones is to reserve assessment until the time of laparoscopic cholecystectomy. Peroperative cholangiography is readily performed using a variety of approaches and is successful in 75 per cent of patients[1]. Peroperative cholangiography also helps to define the anatomy of the extrahepatic biliary tree. If common bile duct stones are detected the options of converting to immediate open cholecystectomy with choledochotomy or subsequent

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endoscopic sphincterotomy and stone removal in the early postoperative period are available.

A more controversial approach to silent common bile duct stones is to abandon screening completely and reserve detailed investigation of the extrahepatic biliary tree for those patients who have historical, clinical or biochemical evidence of choledocholithiasis[10]. The natural history of common bile duct stones has not been clearly defined but it is well documented that many common bile duct stones pass spontaneously and uneventfully through the papilla of Vater[11]. In our experience of laparoscopic cholecystectomy in 100 patients without evidence of choledocholithiasis, and in whom peroperative cholangiography was not performed, one patient developed symptoms related to common bile duct stones postoperatively. Accepting a 10–15 per cent prevalence of silent common bile duct stones, a number of patients in our series are currently harbouring stones in their common bile ducts or have passed them uneventfully into the duodenum. It has recently been recognised that patients with asymptomatic gallstones do not require treatment[12]. Similarly, it may be that patients can be left in possession of asymptomatic common bile duct stones without risk.

G. McEntee
P. A. Grace
D. Bouchier-Hayes

Department of Surgery
Royal College of Surgeons in Ireland
Beaumont Hospital
Dublin
Ireland

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Quadrantectomy for early breast cancer

The continuing debate on the conservative management of breast cancer focuses on the incidence and significance of local recurrence after breast conserving procedures. Local recurrence rates vary from the 5 per cent at 5 years reported by Sarrazin *et al.*[1] to 21 per cent in a recent study from Nottingham[2]. Such variations are a cause for concern and require that close attention is paid to patient selection and the choice of surgical and radiotherapeutic technique if the breast is to be conserved.

The search for optimal management has been helped by recent publication of the long-term results of the Milan trial in which, between 1973 and 1980, 701 women with small breast cancers were randomized to receive either Halsted mastectomy or quadrantectomy with axillary dissection and breast irradiation. The 10- and 13-year follow-up figures show no significant difference between the groups, nor any trend in favour of either group in terms of survival, or the incidence of local recurrence or contralateral disease[3].

A more recent Milan trial comparing quadrantectomy and external radiotherapy with lumpectomy and external plus interstitial radiotherapy has shown higher local recurrence rates in the lumpectomy group at 5 years (7·0 per cent *versus* 2.2 per cent) though no difference in survival rates was apparent[4]. These studies confirm the conclusions of the NSABP study that adequacy of local resection is crucial in minimizing the incidence of local recurrence, and that subsequent radiotherapy cannot be guaranteed to safeguard an inadequate resection from local recurrence[5]. Simple dependence on a pathologist's report of 'clear margins' is insufficient, particularly where there is a large intraductal component to the tumour.

There is a clear relationship between the size of the surgical margin and the risk of local recurrence[6]. The success of quadrantectomy in preventing local recurrence is probably due in part to the generosity of the lateral clearance margins, but may in addition be related to the anatomical wedge that is removed. By encompassing the whole of the involved ductal system it is more likely to remove residual microscopic permeating and infiltrating cancer or *in situ* disease.

The need to establish margins of at least 2 cm makes quadrantectomy technically difficult when dealing with tumours larger than 3 cm unless the breast is itself large. However, the procedure is straightforward and Veronesi's results are valuable reassurance that with appropriate and careful technique, the breast harbouring a small cancer can be preserved without detriment to the patient's survival and with a risk of local recurrence that is no greater than that following mastectomy.

A. E. Young

St. Thomas' Hospital
London SE1 7EH
UK

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Repair and replacement of deep vein valves in the treatment of venous insufficiency

N. M. Wilson, D. L. Rutt and N. L. Browse

Surgical Unit, St. Thomas' Hospital, London SE1 7EH, UK
Correspondence to:
Mr N. M. Wilson

Venous insufficiency is a widespread condition, the prevalence of venous ulceration being 0·5–1·0 per cent in Western populations. A principal abnormality causing venous insufficiency is deep venous reflux, usually resulting from post-thrombotic valve destruction. Patients undergoing treatment for venous insufficiency should have all venous abnormalities investigated, defined and corrected where possible. Although treatment for superficial and communicating vein incompetence is available, correction of deep vein reflux has been neglected until recently. Deep vein valve physiology, the selection of patients for deep vein valve surgery and methods of valve repair and replacement are reviewed.

The prevalence of venous ulceration in European populations is estimated to be 0·5–1·0 per cent[1–4]. Valvular incompetence, outflow obstruction and primary or secondary calf muscle failure are the underlying pathophysiological abnormalities in patients with venous insufficiency. In particular, deep vein reflux has been incriminated as an important cause of venous insufficiency[5–8], some workers claiming that it is the principal causative abnormality in up to 90 per cent of patients with venous ulceration[9].

Valve destruction following post-thrombotic recanalization was described by Homans[10]. In our experience, over 95 per cent of patients with venous ulcers and deep reflux have post-thrombotic disease[11], although primary deep valve incompetence appears to be more common in other centres[12,13].

Deep vein reflux has proved one of the most difficult abnormalities to define and correct. Indeed, the value of deep vein valve reconstruction, particularly at the femoral site, has been brought into question[14,15]. There is good evidence, however, that the correction of reflux in all relevant venous systems in patients with venous insufficiency improves calf pump function and is accompanied by resolution of ulceration and improvement of symptoms[16–18]

Development of vein valve surgery

Carrel and Guthrie reported the autotransplantation of animal valve-bearing vein segments in 1906[19] The development of surgical techniques was then largely neglected until 1947 when Johns undertook further studies of venous anastomosis[20] In 1953 Eiseman and Malette reported the first technique of valve construction[21]. This technique, performed in the canine inferior vena cava, produced a valve by intussuscepting the vessel wall. In 1960, De Weese and Niguidula performed venous valve autotransplantation in the dog[22], but it was not until 1968 that Kistner first described a technique of venous valve repair in man[23].

In 1979, Kistner and Sparkuhl described the technique of valve transposition[24], and in 1982 Taheri *et al* reported the first vein valve autotransplant in man[25]. Since 1985, interest in valve surgery has intensified and a number of reports have appeared describing new valve repair methods and valve replacement techniques using homografts, xenografts and prosthetic materials.

Physiology of the deep valves

Unlike cardiac valves, the activity of vein valves is random and sporadic. When venous blood flow is steady during standing, sitting or performing any other static activity, the valve cusps are open and foot vein pressure is equal to the haemostatic pressure exerted by the column of blood between the foot and the right atrium[26] Only following contraction of one of the muscle pumps[11,27], after which the intramuscular vein pressure falls to zero, do the valves maintain the reduction of venous pressure by preventing reflux. This effect is most pronounced during rhythmical activity such as walking[26], and is most apparent and physiologically significant in the superficial veins. The absence of hypotension in the superficial veins during and immediately after exercise defines the condition of venous insufficiency. The principal muscle pump of the leg effecting venous return during exercise is the calf.

The deep vein valves perform their anti-reflux role at different phases of the calf pump cycle[28] The valves of the communicating veins and the veins downstream to the pump close during calf pump systole in an analogous fashion to the mitral valve. The axial deep vein valves of the popliteal and femoral segments are arranged in series and open during calf pump systole, mimicking the aortic valve In calf pump diastole the action is reversed. Both pump inflow and outflow valves may become incompetent, most commonly secondary to post-thrombotic disease. Because of the size, number and arrangement of these valves, all attempts at repair or replacement have been directed towards the larger, outflow tract valves.

Our understanding of cardiac valve physiology and flow dynamics is now at an advanced stage, in sharp contrast to our knowledge of vein valve function which is still rudimentary. During normal walking the calf pump contracts approximately 40 times per min[11], although this may double during fast walking. Examination of foot volumetry recordings suggests that the stroke volume per step passing through the axial popliteal and femoral segments (and valves) is 10–20 ml. The opening and closing pressures, pressure gradients across valves, closing volumes and regurgitation fractions under varying conditions are all largely unknown. The relationship of valve function to calf pump function and venous insufficiency is understood at only the most basic level.

Investigation and significance of deep venous reflux

Deep vein reflux can be demonstrated by descending phlebography[29] or duplex ultrasound scanning[30], while plethysmographic tests of calf pump function demonstrate reflux[31–34], but cannot accurately localize this to a particular

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venous system. Each of these techniques reflects a different aspect of the flow, pressure and volume abnormalities induced by valvular incompetence. As yet, no investigation provides a satisfactory quantification of pathological reflux in the deep or communicating veins, although attempts are being made to define and quantify deep vein reflux in normal subjects[29,35]. Apart from this diagnostic problem, the significance of proven deep venous reflux remains unclear, reflecting our poor understanding of the pathophysiological flow and pressure processes leading to venous disease. Post-thrombotic deep vein damage, gross reflux and disordered calf pump function can be demonstrated in legs with little or no manifestations of venous disease[36]. It seems that the calf pump can function quite well in the face of severe deep reflux providing the rest of the local venous system is functioning normally[11].

Deep reflux does, however, put an additional load on these local valved systems. When these veins, particularly we believe, the communicating veins, also become incompetent, calf pump failure is very likely to ensue with the onset of lipodermatosclerosis and ultimately, ulceration. Certainly, incompetent communicating veins are found in 70–100 per cent of patients with venous ulceration[8,37–39]. This anomaly of poor calf pump function in the absence of obvious venous disease also suggests that a balance of adverse and protective processes may exist. Various causative mechanisms of venous ulceration have been proposed[40,41], but little is known about the mechanisms that may protect against the adverse effects of prolonged venous hypertension.

Investigations and indications for deep vein valve surgery

Ulceration is the final expression of venous insufficiency and until our techniques are fully developed and proven, correction of deep valve incompetence should not be considered until ulceration has occurred and failed to respond to standard forms of treatment.

Patients should ideally undergo ascending phlebography to demonstrate the state of the deep veins and to exclude major obstruction. Descending phlebography or duplex ultrasound can be used to demonstrate the presence and site of reflux and one of the various plethysmographic methods used to assess calf pump function. When calf pump function tests demonstrate superficial and deep vein reflux without major vein obstruction, conventional superficial and communicating vein surgery is indicated. These measures, together with the provision of graduated compression hosiery, will prevent ulcer recurrence in a large proportion of patients[42].

A distinct group of patients exists, however, who suffer persistent ulceration despite these measures Many have significant deep reflux (grade 3–4) on descending phlebography with grossly abnormal calf pump function after conventional superficial and communicating vein surgery. It is this group that is most likely to benefit from deep vein valve surgery.

Raju and Fredericks[43] report that 75–88 per cent of legs with venous ulceration have pure deep vein reflux and suggest that communicating and superficial vein reflux are usually secondary phenomena. Taheri *et al.*[44] also emphasize the important role of deep vein reflux in the pathogenesis of the calf pump failure syndrome. Both of these groups suggest that provision of competent deep vein valves alone is sufficient for its correction in the majority of cases. It is, however, important to emphasize that the repair of one abnormality, in isolation, is likely to be over-stressed and fail. For example, Eriksson and Almgren demonstrated that correction of superficial femoral vein reflux in the presence of profunda vein reflux resulted in very little improvement of venous function, whereas correction of superficial femoral vein reflux in the presence of a competent profunda system resulted in marked improvement of the post-exercise foot vein pressure reduction[18]. Similarly, where communicating, deep and superficial vein incompetence co-exist, all abnormalities should be corrected. This approach has been adopted by Sottiurai who reserves deep vein valve surgery for patients who have proved refractory to all other conservative and surgical measures[45,46].

Valve abnormality: valve repair or replacement?

Valves may be damaged by thrombosis, stretched (floppy) valve cusps and/or valve sinus dilatation, or may be congenitally absent.

Valve repair (valvuloplasty) and replacement are quite distinct techniques and are, to an extent, suitable for different groups of patients. To achieve effective valve repair, the basic structure of the valve must be intact The abnormality most suited to this kind of procedure is non-thrombotic valve incompetence. This may be caused by valve cusp prolapse ('floppy valve cusps') as described by Kistner[12], or valve ring dilatation[9,47] or a combination of the two. Whether or not these are two distinct conditions remains unclear They may represent a primary defect, or may be secondary to, or associated with post-thrombotic damage in the more distal calf veins[12,35]. Raju has suggested that such deep vein thrombosis may be a secondary event to venous reflux consequent on a primary valve abnormality[9]. Whatever its aetiology, non-thrombotic valve incompetence appears uncommon in comparison with post-thrombotic incompetence. Although it has been recognized and treated by a number of other groups[43,48,49], we find great difficulty in identifying it.

Direct post-thrombotic valve damage invariably destroys the valve cusps beyond repair, making them unsuitable for valvuloplasty. In this situation and valve agenesis[50,51], valve replacement techniques are the only suitable procedures We believe, therefore, that valve mechanism replacement techniques are likely to be most widely applicable in the correction of deep venous reflux.

Principles and aims of venous valve surgery

The requirements for effective deep vein valve surgery in the treatment of venous insufficiency are as follows:

1. Demonstration of significant deep vein reflux with impaired calf pump function refractory to conventional superficial and communicating vein surgery
2. Adequate definition and proof of correction of significant co-existing venous abnormalities contributing to the venous insufficiency
3. A valve with physiological static and dynamic properties
4. Avoidance of thrombosis
5. Maintenance of long-term competence.

Valve repair techniques

Valve repair techniques aim to prevent reflux by producing secure cusp apposition without cusp prolapse. Direct valvuloplasty achieves this by shortening the redundant floppy valve cusp edges, while the indirect methods narrow the dilated valve sinus to produce greater cusp contact.

Direct valvuloplasty· valve cusp procedures

Direct valvuloplasty was first described by Kistner in 1968[23] Incompetent, redundant cusp edges are tightened by fine sutures that reef-in the two commissures, restoring competence to the valve unit. Kistner advocates perioperative anticoagulation with heparin and continuation of this for 2 weeks after operation, followed by oral anticoagulation for 2 months. In 1982, Ferris and Kistner reported the late results of 31 valvuloplasty procedures and showed that competence was restored to the majority of these valves and was sustained for up to 13 years when assessed by descending phlebography[16]. Calf pump function was improved, but the effect on clinical venous disease is more difficult to interpret since most of these patients also underwent communicating vein surgery. Indeed, Kistner states that the best results were seen in patients undergoing total correction of the various refluxing systems[12] and it seems that this approach of correcting all abnormalities is most likely to confer lasting benefit.

Raju and Fredericks have performed Kistner's valvuloplasty technique on 61 patients[43]. Of these patients 40 had ulceration and at follow-up of 2 years minimum, 63 per cent of these patients were free of recurrent ulceration. A total of 60 patients had pain and swelling and complete or partial relief of these symptoms was achieved in 87 per cent and 83 per cent respectively at late follow-up. Of the 61 patients, 25 wore compression stockings after operation and a small but undefined number underwent communicating and/or superficial vein surgery A further ten patients underwent valvuloplasty with external Dacron® (E.I. du Pont de Nemours and Company) sheath support in an attempt to prevent dilatation and incompetence of the repaired valve Two or more years after operation, six of the ten patients had improvement of pain and swelling and three of the six patients with ulcers initially were free from recurrent ulceration Calf pump function was improved in both groups compared with preoperative values but there was no significant difference between the patients with and without Dacron cuff external support. These results suggest that the Dacron cuff was of no benefit, although no phlebographic or duplex data concerning valve competence are available.

Eriksson and Almgren have also investigated the long-term results of valvuloplasty in 27 limbs and studied the competence of the repaired valves as assessed by Doppler and phlebographic examination[13]. Valves were repaired at various sites including the common and superficial femoral veins, profunda femoris and popliteal veins. At a mean follow-up interval of 49 months, 19 of the 27 valves (70 per cent) remained competent.

Perrin *et al.* have performed 17 valvuloplasty procedures, 15 of which were assessed for competence phlebographically or with Doppler ultrasound at a median interval of 28 months[52]. Thirteen valves were competent, and this series again emphasizes the high rate of competence obtainable in the long term with this procedure.

Minor modifications of Kistner's technique have been described recently, Raju and Fredericks advocating a transverse venotomy to gain access to the redundant cusps in preference to the original vertical incision[43], Sottiurai employing a combination of the two, using a T-shaped incision[45]. Using this technique, Sottiurai reported 100 per cent valve competence in 20 patients at mean follow-up of 37 months. All of these patients underwent superficial and communicating surgery.

Indirect valvuloplasty: valve sinus procedures

In 1972, Hallberg reported a technique to reduce sinus dilatation by wrapping a Dacron cuff around the valve[47]. The diameter of the cuff was adjusted to restore valve competence. One patient with chronic venous ulceration (despite superficial and communicating vein surgery and bandaging) was treated in this way and patency and competence were demonstrated phlebographically at 2 months. Clinical improvement apparently occurred during this short period, although details of long-term follow-up were not available. Raju and Fredericks have employed the technique in 12 patients, eight of whom had venous ulceration[43] By 2 or more years after operation, ten patients had improvement of pain and swelling and five patients were free from recurrent ulceration.

Jessup and Lane have recently investigated a similar technique in the external jugular vein of the sheep where a Dacron-reinforced silicone cuff (Venocuff®, Vaso Products Pty, Ltd., NSW, Australia) was used to resolve natural or induced valve incompetence[53]. The cuff restored competence in most valves, but was surrounded by a fibrous capsule and induced a mild fibrosis of the vein wall, although the endothelium remained intact

Axial plication of the valve sinus has also been employed to reduce excessive dilatation and restore valve competence. Jones *et al.* performed this procedure in five patients with chronic venous disease and achieved resolution of oedema and ulceration up to 1 year[49].

Direct valvuloplasty apparently confers lasting competence in the majority of valves, together with long-term improvement of calf pump function and resolution of clinical disease when combined with other appropriate procedures. Meticulous technique is required, and considerable measures are necessary to avoid thrombosis. The great advantage of indirect valvuloplasty techniques is that they do not require a venotomy and leave no foreign material within the lumen. Clamping of the vein is avoided, and heparinization and other antithrombotic measures are unnecessary. The long-term effects of a cuff on the valve wall are not yet clear.

Both direct and indirect valvuloplasty techniques are likely to be of limited use as most deep vein reflux is caused by post-thrombotic valve destruction, but they may well be of use in valve transposition or transplantation procedures, in maintaining or restoring competence.

Valve mechanism replacement techniques

A considerable number of valve mechanism replacement techniques have been described in animal studies, but relatively few have been attempted in man.

Valve transplantation

Although Carrel and Guthrie transplanted valve-bearing vein segments in the dog[19], it was not until 1960 that De Weese and Niguidula specifically studied the fate of autotransplanted valves[22]. They transplanted femoral vein valves from the contralateral leg in 20 dogs achieving primary patency, 14–21 days after implantation in 11 with competence in nine, as assessed by Harvey's test[54]. They demonstrated that early thrombosis followed by recanalization could give a false impression of patency but that where this occurred the valve was always incompetent During the 1960s further animal studies followed, particularly evaluating the role of autotransplanted valves in healthy and experimentally thrombosed veins[55–59] These studies demonstrated that valve autotransplantation was a practical proposition, and in 1982 Taheri reported the first human procedures involving transplantation of a brachial vein valve into the superficial femoral vein of patients with post-thrombotic reflux[25]. This procedure was performed with full systemic heparinization followed by oral anticoagulation for 3–6 months. Latterly, Taheri has used pneumatic compression to prevent thrombosis and abandoned postoperative anticoagulation. Since 1983, he has placed the transplantated valve in the popliteal vein rather than the femoral vein[60].

In 1985, Taheri *et al.* reported the results of 71 valve transplants performed over a 5-year period in patients with severe symptoms refractory to conservative measures, grade 3 or 4 reflux, elevated venous pressures, and muscle changes[44]. Follow-up was conducted by consultation, postal survey, and telephone enquiry. Forty-eight patients responded. A total of 36 patients reported improvement or complete relief of symptoms and 17 of the 18 responders with leg ulceration reported healing Foot vein pressure measurements were performed before and after operation in only 20 patients. The average improvement of pressure reduction during exercise was 13 per cent, i e all the patients still had abnormal calf pump function, and two patients' exercising venous pressures were increased. Postoperative descending phlebography was performed in 31 patients. Twenty-eight valves were judged patent and competent, one was occluded and two were incompetent How long after transplantation these limited, objective studies were performed is unclear. It is also unclear how many patients had previously undergone superficial and communicating vein surgery.

Nash has recently reported the results of 25 valve autotransplant procedures from the brachial to the popliteal vein in 23 patients with post-thrombotic reflux[17]. All patients had persistent ulceration or skin changes despite previous superficial and communicating vein surgery. Of 17 patients 15 healed their ulcers and six patients with skin changes showed rapid healing with resolution of symptoms. Ambulant venous pressure fell by an average of 18 per cent after operation and this improvement was sustained in most patients 18 months later when all 18 valve transplants were patent, although five showed phlebographic evidence of reflux.

Raju and Fredericks have also reported the results of valve autotransplantation to the superficial femoral vein in 18 patients and a further six patients who had an adjunctive Dacron cuff secured around the transplanted valve[43]

Six of the 13 patients with ulceration in the former group were free of recurrent ulceration 2 or more years later and two of the six patients with ulceration in the later group remained healed at the same interval.

Eriksson and Almgren have studied the function of 34 autotransplanted valves at a mean interval of 27 months after operation using descending phlebography and duplex scanning[13]. Valves were transplanted to the common or superficial femoral and popliteal veins. Of the valves 11 were competent, 16 were incompetent and eight were thrombosed. These results are of interest for a number of reasons. First, direct assessment of valve function provides a more accurate account of the procedure's efficacy than subjective assessment of symptomatic relief and even objective observations of freedom from recurrent ulceration Second, the relatively low rate of competence and high rate of thrombosis are at variance with the other series discussed, most of which have achieved surprisingly low rates of thrombosis, in particular.

Perrin *et al.* have achieved similar results in a series of 21 valve autotransplant procedures, 17 of which were assessed at a median interval of 28 months postoperatively[52]. Only six valves were free from significant reflux when assessed phlebographically or by duplex scanning.

Venous valve transplantation is undoubtedly successful in correcting reflux and improving calf pump function in the short-term and is associated with the resolution of ulceration and symptoms in some patients. Virtually all series confirm that the procedure is inferior to valvuloplasty, although this finding should be seen in perspective as the valve vein defect is quite different in the two groups. Undoubtedly, the symptoms, signs and impairment of venous function, together with valve incompetence, tend to recur as time passes[61].

Obtaining a suitable valve for transplantation can be troublesome. Raju and Fredericks have found that 30–40 per cent of axillary vein valves are incompetent before harvesting[43], while Sottiurai finds that 40 per cent of harvested valves are incompetent once transplanted, despite being competent at preoperative descending phlebography[46]. Such valves require adjunctive valvuloplasty.

In an attempt to overcome the limitations of valve supply inherent in autotransplantation, interposition of glutaraldehyde-preserved homografts and xenografts has been attempted[62,63]. Low patency and competence rates have so far precluded the use of these techniques in man.

Brachial and axillary valve autotransplants tend to fail with the passage of time[9]. Possible reasons for this are: size mismatch between the transplanted valve and recipient vein resulting in valve dilatation and incompetence – even in the popliteal position[17]; shedding of valvular endothelium during the first 4 months following transplantation, resulting in thrombosis and/or incompetence[64] and late fibrosis and degeneration, possibly caused by ischaemia[65]. On one occasion when we considered valve autotransplantation in a patient with venous insufficiency and ulceration caused by valve aplasia, phlebography revealed a total absence of brachial valves. Such problems make valve autotransplantation unsuitable for universal use in the correction of deep venous reflux.

Valve transposition

In 1979, Kistner and Sparkuhl described the technique of valve transposition. This involves transposing a competent valve-bearing segment of long saphenous vein (end-to-end anastomosis), or profunda femoris vein (end-to-side anastomosis), on to the incompetent superficial femoral vein[24]. This technique was performed in 14 patients all of whom had grade 3 or 4 reflux[16]. Reflux and foot vein pressures were improved in all patients initially, but by 3 years, several had recurrence of their reflux, and many had recurrent symptoms. One of the criticisms of this study has been that most of the patients underwent communicating vein surgery, which may have masked the effect of the transposition[11,66]. Consequently, Queral *et al.* performed a similar study in 12 patients but performed only the transposition procedure[67].

Three months after operation, the mean postexercise foot vein pressure recovery time had returned to normal and all ulcers had healed. At 1 year, however, the mean recovery time had become abnormal and nine patients had developed recurrent ulceration[68]. All these patients had gross communicating vein reflux. Unfortunately, only two patients underwent late descending phlebography, and thus, the performance of the transposed valves is impossible to assess.

Perrin *et al.* have performed the transposition procedure in six patients who also underwent superficial and communicating vein surgery where indicated. At median follow-up of 28 months, 50 per cent of transposed valves were grossly incompetent[52].

Kistner's study failed to demonstrate the value of valve transposition in the restoration of calf pump function, and suggests that subsequent deterioration is largely due to failure of the transposed valve. Queral's study, however, shows that valve transposition alone can restore calf pump function to normal, thus suggesting that deep reflux is of major importance in determining calf pump function, but fails to demonstrate whether the recurrence of calf pump failure in this study was caused solely by deteriorating communicating vein reflux or failure of the transposed valve. The evidence published to date suggests that the insertion of a functioning valve in the femoral vein by transposition improves calf pump function initially, but fails to confer long-term deep axial vein competence, and does not compensate for superficial and communicating vein reflux.

Psthakis' substitute valve

Psthakis first performed the substitute valve technique in 1963, employing a sling fashioned from the gracilis muscle to externally compress the popliteal vein during walking[69].

Fibrosis and adhesion formation prompted him to modify the technique, and he now uses a Silastic® (Dow Corning, Reading, UK) strip sutured to the gracilis tendon. He has recently claimed excellent late phlebographic, functional, and clinical results in 145 patients[70]. This technique has been evaluated in a few other centres, and their early results do not match those of Psthakis[51,72].

Experimental valve mechanism replacement techniques

Over the past 5 years, interest in alternative valve replacement techniques has increased This has been provoked by increasing awareness of the prominent role of deep reflux in venous insufficiency and failure of the currently available techniques to provide long-term patency and competence, particularly in post-thrombotic reflux. Most of these techniques have been described in single case reports or animal studies.

Case reports

Garcia-Rinaldi *et al.* have implanted a xenograft monocusp valve mechanism in the superficial femoral and long saphenous veins of a patient with chronic venous ulceration refractory to conservative treatment in whom descending phlebography and Doppler examination had revealed gross deep and superficial reflux[72]. The monocusp valves were constructed using preserved bovine pericardium and incorporated into the vein wall. Descending phlebography 4 weeks after operation demonstrated full competence, as did Doppler examination at intervals up to 14 months. Photoplethysmography performed

14 months postoperatively suggested normal calf pump function. Ulceration and symptoms resolved without the use of compression stockings. The patient was anticoagulated for 6 months.

Simpkin *et al.* have described the construction of a choke mechanism in the femoral and popliteal veins by the creation of a stenosis[73]. Although not strictly a valve, this is said to impede deep reflux, but no evidence is presented to confirm this claim. The clinical results in the four patients concerned are obscure. The mechanism seems just as likely to produce outflow obstruction as reduce reflux.

Sloan has recently reported the use of a cryopreserved infant pulmonary valve homograft[74]. This was placed in the common femoral vein of a patient with post-thrombotic ulceration. Symptoms and ulceration had resolved 6 months later but no details of late patency, competence or calf pump function are available. This technique depends on a supply of infant cardiac valves and cryopreservation techniques, neither of which is yet widely available in the UK.

Animal studies

In 1953, Eiseman and Malette[21] used the principle of wall intussusception as described by Perl[75] to produce a caval valve in 14 dogs. No anticoagulation was used and no gross thrombosis was found between 24 h and 6 months later. Descending phlebography via the right renal vein was used to demonstrate competence of the valves, but no results are presented.

Hill *et al.* have designed a bicuspid flutter valve mechanism which has been produced in both pellethane polymer and tanned human umbilical vein[76]. Ten pellethane and ten umbilical vein valves were implanted into the external jugular veins of 20 dogs. The umbilical vein valves were all occluded by 48 h, and all the pellethane valves were thrombosed by 8 days, in spite of full anticoagulation.

In 1985, Ackroyd implanted glutaraldehyde-preserved homograft valves in the canine femoral vein[62]. Despite adjunct procedures such as peroperative heparinization (seven dogs), defibrinogenation (three dogs), and the construction of an arteriovenous fistula (eight dogs) all preserved valves had thrombosed by 6 weeks. In a similar study, Kaya *et al* found that glutaraldehyde-preserved valve autografts had superior patency and competence with preserved homografts at 7 weeks[63].

Warmenhoven *et al.* have implanted valve-shaped Silastic mandrels in various positions in dogs to excite the production of a corresponding collagen sheath[77]. After 5–13 weeks, the mandrel was removed and the collagen valve removed for implantation into the femoral or external jugular vein. A total of 15 valves were produced in this way and inserted without anticoagulation All valves had thrombosed 16 weeks after implantation

In 1988, Rosenbloom *et al.* described a method of valve contruction using autologous external jugular vein in the dog[78] A segment of external jugular vein was harvested and the media and adventitia partially stripped from the intima which was then invaginated and secured to produce a cusp mechanism. The resultant valve was then interposed in the canine femoral vein. A total of 15 such valves were constructed The pressure gradient required to open the valve (opening pressure) was less than 3 cmH_2O in the three valves that were studied, and the closing pressures of two valves 3–5 cmH_2O. Four valves remained competent at pressure gradients of 55 cmH_2O. After implantation in six non-heparinized dogs, thrombus formation prevented cusp closure, leading to incompetence in four, whereas the valves implanted in three anticoagulated dogs stayed patent and competent for 13 days after implantation. This is one of the few studies to give an account of the hydrostatic properties of a constructed valve, showing that it will function within the physiological range.

The limitations of autogenous vein valve autotransplantation, including inadequate donor valves and late cusp degeneration[65], have prompted Taheri to develop a metal valve mechanism[79]. He has designed a centre-hinged bileaflet valve in platinum or pyrolite carbon-covered titanium. These valves were initially tested for fatigue and wear characteristics over a 5-month period. One valve showed cracking adjacent to a cusp hinge. Hydrodynamic pressure and flow studies showed regurgitation of approximately 48 per cent of the ejected stroke volume per cycle in the first few valves, although this improved subsequently Ten valves (five of each material) were then implanted into nine dogs, seven in the inferior vena cava and three in the femoral vein All five titanium valves showed evidence of thrombosis with complete occlusion of four between 14 and 18 months after implantation. Two of these valves also became grossly displaced. The four platinum valves studied phlebographically were patent and competent 14–18 months after implantation[65]. Problems such as displacement, regurgitation and thrombosis seem to preclude any human trial at present.

Phifer *et al.* have implanted cardiac bioprosthetic xenograft valves in the inferior vena cava of 22 dogs and have recently reported their late results[80]. Despite promising early results[81], ten valves had thrombosed by 28 months and nine had caused pulmonary emboli. Six of the eight patent valves examined with descending cavography were thought to be partly competent but this was not quantified and at autopsy, the majority of the cusps of these valves were adherent to the cava wall

Spiegowski *et al.* have recently described a variety of techniques for the autotransplantation of valve cusps from the brachial to the femoral vein in dogs[82]. Where cusps were transplanted on a vein patch, 100 per cent patency was achieved at 10–16 weeks post-implantation and 80 per cent of valves were competent after the same period, although only at the relatively low pressure gradient of 16 mmHg. Isolated cusp transplantation was associated with a poor degree of patency.

Spiegowski *et al.* have also reported their experience of valve segment autotransplantation in the dog[83]. In addition to the usual end-to-end anastomosis technique, they have also placed the valve segment in parallel to the recipient vein using biterminal end-to-side anastomosis. Using this technique, 80 per cent patency and competence was achieved after 4 months This compares favourably with the 80 per cent patency and 70 per cent competence rates attained using conventional end-to-end anastomoses. These figures illustrate the important distinction between patency and thrombosis. Of the valves that were patent 12·5 per cent were incompetent because of thrombus adjacent to the cusps

Van den Broek has recently described a microsurgical technique involving the creation and implantation of an autogenous peritoneal monocusp mechanism in rats[84]. Although the valves remained patent and free from thrombosis, few were competent.

In many of these animal studies it appears that homografts, xenografts, prosthetic materials and the use of glutaraldehyde preservation excite an unacceptable degree of thrombosis. Until control of antigenicity and non-thrombogenic preservation techniques are available, these methods are unlikely to be of use in man. At present, autogenous venous endothelium appears to be the ideal material for valve replacement. In addition to the problems of availability and size-mismatching, valve autotransplantation causes devascularization of the vein wall, sinus and/or cusps, together with extensive endothelial cell shedding which begins within 20 min of removal and persists for up to 4 months post-implantation[64]. To overcome these problems, we have developed a technique of vein wall intussusception and studied it in the canine femoral vein[85]. This technique produces a size-matched, autogenous venous valve constructed from living, vascularized endothelium. A total of 41 valves have been fashioned in veins of 3–10 mm diameter. Immediate phlebographic studies have shown full competence in 39 valves and bench studies indicate complete competence to pressure gradients of 0·2 to 250 cmH_2O in 24 of the 27 valves assessed. Opening and closing pressure gradients in both *in vivo* and dynamic bench studies are less than 5 cmH_2O. Six valves studied from 1 to 112 days post-implantation in non-anticoagulated dogs have remained patent with no evidence of thrombosis. Descending phlebography showed competence in five of these valves. Studies are currently underway to assess long-term patency and competence.

Venous valve surgery: the future

The problems highlighted by the studies described above are:

Demonstration of degree and significance of deep venous reflux

In order to assess our results we need better methods of measuring reflux so that each individual problem can be described and characterized. In particular we need to be able to distinguish between physiological and pathological reflux.

Adequate definition and correction of co-existing venous abnormalities

Many of the above studies seem to suggest that optimum surgical treatment of venous insufficiency requires the correction of all abnormalities. Improved methods for detecting communicating vein incompetence are needed and the effects of their ligation must be more carefully assessed. Whenever deep vein surgery is performed, the state of the superficial and communicating veins must be accurately described together with any procedures performed upon them.

Production of a valve with physiological hydrostatic and hydrodynamic properties

In comparison with cardiac valves (native, bioprosthetic and prosthetic) very little is known of the flow and pressure properties of venous valves. The behaviour of venous valves is complex in that regular repeated action occurs only during walking or running. Most other activities cause random, irregular valve action. Thus, static and dynamic studies are required to characterize the properties of native valves and any new valve mechanism that may be devised.

Avoidance of thrombosis

It appears that autogenous venous endothelium is the material least likely to be affected by thrombosis. Techniques such as anticoagulation[23,25], mechanical calf compression[60] and formation of arteriovenous fistulae[86] have been used to protect against thrombosis, but some may have adverse effects on the valve cusps. New materials and techniques such as endothelial cell seeding may further improve patency rates, but will need extensive testing to prove their antithrombosis properties.

Maintenance of long-term competence

Thrombosis, sinus dilatation, autogenous tissue viability, fatigue, and wear and tear in preserved and prosthetic materials, all appear to be important factors in long-term valve function. These problems can only be assessed by long-term *in vivo* studies

How many valves are needed and where?

In addition to producing a valve mechanism that retains long-term competence, it is necessary to define the site and number of valves necessary to provide the optimal improvement of calf pump function. At present the problems associated with single valve repair or replacement are sufficiently challenging to preclude multiple procedures, but it does seem that the popliteal position is preferable to the femoral[14,87–89].

Increasing interest in venous disease and, in particular, deep venous reconstruction is already yielding solutions to some of these problems. Venous valve surgery may well become a part of the vascular surgeon's repertoire in the foreseeable future

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Review

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Watermelon stomach

R. H. R. Park and
R. I. Russell

Gastroenterology Unit, Royal
Infirmary, Glasgow G31 2ER, UK
Correspondence to:
Dr R. H R. Park

The typical and atypical appearances of watermelon stomach (gastric antral vascular ectasia) during endoscopy, along with the treatments for it, are reviewed.

The early pathologists, the high priests of gastrology (the users of culinary terms in medicine)[1], would have approved of the term watermelon stomach Undoubtedly they would have welcomed the watermelon stomach into their museums, alongside nutmeg livers and sago spleens. A term coined by Jabbari *et al.* in 1984, watermelon stomach describes the endoscopic appearances of longitudinal gastric antral folds containing visible vessels radiating from the pylorus (gastric antral vascular ectasia)[2]. The longitudinal stripes resemble the skin of a watermelon.

Watermelon stomach is a distinct clinical entity within the spectrum of upper gastrointestinal mucosal vascular abnormalities[3]. The macroscopic abnormalities are confined to the antrum. Histological examination demonstrates specific features including hyperplasia of the gastric mucosa, dilated mucosal capillaries, focal thrombosis and fibromuscular hypertrophy of the lamina propria. Jabbari *et al.*[2] described three cases of severe chronic iron deficiency anaemia due to gastrointestinal blood loss. Subsequently many other reports have appeared in which several patients have required multiple blood transfusions (up to 30 units) over 5–10 years[4–19]. Interesting associations with watermelon stomach include a high incidence of female, elderly patients (60–70 per cent of cases)[2,9,14,18], achlorhydria (35 per cent)[2,7,9,10,13,17,20], chronic liver disease (40 per cent)[2,4,5,9,11,13,14,17,18,21] and lymphoma (two cases only)[19] In many cases the endoscopic appearances are not of the classical watermelon stripes but of diffuse gastric reddening[2,4,11,13,14,19,22].

Is this a new clinical problem or has it simply been overlooked? The latter is more likely In 1953 Rider *et al.* described a similar clinical problem in which the gastric antral mucosal vascular problem was more diffuse[20]. Two other reports predated Jabbari's description[21,22]. Endoscopists will continue to miss the diagnosis if antral mucosal abnormalities (red stripes, red spots, diffuse reddening) are attributed solely to antral haemorrhagic gastritis. Biopsies will confirm the correct diagnosis, as characteristically there is very little inflammation on histological examination. Although antral gastritis may cause bleeding, it should never be the explanation for severe, recurrent gastrointestinal bleeding, a situation which should alert the clinician to the possibility of antral vascular ectasia. Angiography has been found to be unhelpful[13,15,18,21] and the diagnosis rests with an awareness of the condition at the time of endoscopy and biopsy confirmation. Although watermelon stomach was considered to be an exotic rarity, we have identified five cases within the routine endoscopic workload of our unit over an 18 month period[19].

Jabbari *et al.*[2] proposed that recurrent gastric antral mucosal prolapse could explain the macroscopic and microscopic findings. In one of their resected gastric antral specimens, the mucosa was loosely attached to the underlying muscularis externa. Several cases have been associated with achlorhydria, and Borsch[14] has hypothesized that the secondary hypergastrinaemia[23] may be trophic to the spindle cell population in the gastric antrum producing fibromuscular hypertrophy. Other reports have found an association wth chronic liver disease and cirrhosis (chronic active hepatitis[2,21], primary biliary cirrhosis[5,19] and alcoholic liver disease[18,19]) Watermelon stomach may be another example of portal hypertensive mucosal vasculopathy[24].

How should the watermelon stomach be managed? Initial reports proposed two options conservative management with repeated blood transfusions and drugs, or antrectomy, the definitive cure, which gave excellent results in fit patients[2,4,9]. However, there is an operative mortality rate of 7·4 per cent for this operation[14]. Steroids have been tried in four patients with some success[2,9,13,20], and tranexamic acid reduced the blood transfusion requirements in a patient with alcoholic liver disease[19]. H_2-receptor antagonists and sucralfate have been uniformly unsuccessful in treating the gastric bleeding[2,7,19]. There is a single case report of the unsuccessful use of radiotherapy[21]. Therapeutic endoscopy now seems to be the treatment of choice. Endoscopic laser therapy[11,15,16,18,19], heater probe therapy[17] and injection sclerotherapy using alcohol[12] have all successfully ablated the antral lesions and controlled the chronic gastric bleeding. The disadvantages are the frequent endoscopic sessions (three to six per patient) and the likelihood of recurrence as the underlying mechanism has not been removed. As yet the results do not include long-term follow-up. Hopefully, one of these endoscopic techniques may avoid the need for surgery in patients with watermelon stomach

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Carotid endarterectomy in Great Britain and Ireland: trends and current practice

J. A. Murie and
P. J. Morris*

*Vascular Surgical Unit, The Royal Infirmary, Edinburgh EH3 9YW, UK and *Nuffield Department of Surgery, John Radcliffe Hospital, Oxford, UK*

Correspondence to:
Mr J. A Murie

Of 309 questionnaires on carotid endarterectomy sent to all surgeons in Great Britain and Ireland who might use this technique, 298 (96 per cent) were returned. In all, 110 (37 per cent) of 298 surgeons performed at least one carotid endarterectomy in 1989; 67 performed <10 and 43 >10. In total, these 110 surgeons performed 1417 operations in 1989, a situation that has changed little over 5 years since the previous survey. Transient ischaemic attack and minor stroke remain the main indications for carotid endarterectomy; the operation was hardly ever performed for asymptomatic stenosis. By 1989 almost all surgeons initially assessed prospective patients using a technique less invasive than conventional angiography; duplex scanning was used 'always' or 'sometimes' by 70 per cent of surgeons. While 72 per cent of surgeons in 1984 'always' required conventional angiograms before operation, by 1989 only 21 per cent did so, most now relying on less invasive techniques. During operation there was an increasing use of shunts, carotid sinus nerve blockade and patch closure of the arteriotomy. The overall number of carotid endarterectomies performed annually in Great Britain and Ireland has remained steady over the past 5 years and is relatively low for a population of 60 millions. An increase in the number of surgeons performing the operation is almost entirely accounted for by an increase in those performing <10 carotid endarterectomies per year.

The seminal operation which provided the impetus to carotid surgery worldwide was carried out by Eastcott *et al.*[1] at St. Mary's Hospital, London on 19 May 1954 and, although 36 years have passed, the role of carotid endarterectomy for patients at risk of stroke still owes more to fashion than to science. Fortunately, international prospective randomized studies are underway, although no results have been reported in the literature.

For the present, the status of carotid endarterectomy largely depends on the expressed opinions of experienced vascular surgeons and neurologists, both here and abroad In recent years, there has been much discussion in the world literature about the operation and this article is an attempt to describe how surgeons in Great Britain and Ireland have responded This is possible because the present study uses a questionnaire similar to that used in a previous report[2,3] which described carotid endarterectomy in Great Britain and Ireland in 1984. The data obtained from the present questionnaire allow a description of current practice, while comparison with the previous data allows trends to be recognized.

It is inappropriate here to describe all the contentious issues which surround carotid endarterectomy but two features are worth mentioning. First, in the USA the number of carotid endarterectomies performed annually increased dramatically to a peak of 107 000 in 1985; this was followed by a sudden decline[4] of 22 per cent in 1986. Pokras and Dyken have suggested that this decrease was the result of the considerable adverse comment in the literature between 1984 and 1986 on the widespread use of carotid endarterectomy[4–16] The present study describes the number of carotid endarterectomies currently performed in Great Britain and Ireland and the numerical trend.

Second, it is understood that for carotid endarterectomy to be of value as a prophylactic procedure it must have minimum perioperative morbidity and mortality A combined morbidity and mortality rate up to 10 per cent might be regarded as acceptable[15]. To achieve the best results requires substantial carotid artery operating experience[17,18] and the present study describes the annual experience of individual surgeons and the trends in experience between 1984 and 1989

A variety of other subjects are examined including the nature of patient referral for surgery, the accepted indications for operation, the impact of advances in imaging technology[19], and technical details of the operation.

Materials and methods

A questionnaire was sent to 309 surgeons in Great Britain and Ireland who might perform carotid endarterectomy in their practice This group comprised the 303 current members of the Vascular Surgical Society of Great Britain and Ireland and six neurosurgeons known to use the operation. The number of operations each surgeon had performed, or had caused to be performed by an assistant, in 1989 was requested and the following nine questions were asked Possible responses are given in parentheses This survey of 1989 activity was similar to that carried out for 1984[2]

1 Referrals for possible operation came from which of the following sources? [often, sometimes, rarely, never]
   Family doctor (direct)
   General physician
   Neurologist
   Ophthalmologist
   General surgeon
   Other (give details)
2. Which of the following were indications for carotid endarterectomy? [often, sometimes, rarely, never]
   Asymptomatic bruit
   Transient ischaemic attack including amaurosis fugax
   Minor stroke (>24 h, <7 days)
   Stroke (>7 days)
   Other (give details)
3. Which screening techniques excluding conventional angiography were used for potential surgical candidates? [always, sometimes, rarely, never]
   Oculopneumoplethysmography

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Phonoangiography
Duplex scanning
Ultrasound imaging (alone)
Ultrasound spectral analysis (alone)
Supraorbital Doppler ultrasonography
Intravenous digital subtraction angiogram
Intra-arterial digital subtraction angiogram
Other (give details)

4 Which angiograms were obtained prior to surgery? [always, often, rarely, never]
Conventional angiogram
Intravenous digital subtraction angiogram
Intra-arterial digital subtraction angiogram

5. Operations were performed under which type of anaesthetic? [always, sometimes, rarely, never]
Local anaesthesia
General anaesthesia

6. What type of shunt (if any) was used? [always, sometimes, rarely, never]
Javid
Pruitt
Other (give details)

7 If a shunt was used 'sometimes' or 'rarely' what was the criterion (or criteria) for its use?
Electroencephalogram or cerebral monitor change
Paresis (under local anaesthesia)
Low stump pressure (give details)
Other (give details)

8 Was the carotid sinus nerve blocked with local anaesthetic? [always, sometimes, rarely, never]

9. Was the arteriotomy closed with a patch? [always, sometimes, rarely, never]
Vein
Polytetrafluoroethylene (PTFE)
Dacron®

Although minor alterations have been made to a few of the questions compared with the 1984 version, most are the same. This has ensured that a direct comparison with much of the 1984 survey is possible.

Results

Of the 309 questionaires sent, 298 (96 per cent) were returned, the same proportion as in the 1984 survey. Of the surgeons who replied, 110 (37 per cent) had performed at least one carotid endarterectomy in 1989; 67 (61 per cent) of these 110 carried out $\leqslant 10$ and 43 (39 per cent) had carried out > 10. The corresponding figures for the 96 surgeons who performed the operation in 1984 were 56 (58 per cent) and 40 (42 per cent) respectively (*Table 1*).

The commonest source of referral for carotid endarterectomy was neurologists (*Table 2*). Direct referral from family doctors occurred 'often' in the practice of only 20 surgeons. Although general physicians and ophthalmologists also referred patients, very few came from general surgeons or other sources such as cardiac surgeons and geriatricians. It is also surprising that there were few referrals from vascular surgeons who do not perform carotid endarterectomy to those who do. It may be that local referral patterns generally favour the latter group of surgeons or, perhaps, some vascular surgeons dislike carotid endarterectomy and use only medical treatment for patients at risk of stroke. In any event, the overall pattern was very similar to that of 1984.

The commonest indication for carotid endarterectomy remained carotid territory transient ischaemic attack, for which all surgeons performed the operation 'often' or 'sometimes' (*Table 3*) The only other numerically significant indication was minor stroke for which 64 (58 per cent) surgeons performed carotid endarterectomy 'often' or 'sometimes'. Operation for asymptomatic bruit was rare. Overall, there was little discernible change in indications for operation between 1984 and 1989.

In 1989, only four (4 per cent) surgeons 'rarely' or 'never' used a screening technique for potential surgical patients which was less invasive than conventional angiography; all four performed < 10 carotid endarterectomies In 1984, 12 per cent of surgeons 'rarely' or 'never' used such an assessment. Duplex ultrasonography has become the clear leader in carotid screening technology, despite their invasive nature the only other techniques frequently used were intra-arterial and intravenous digital subtraction angiography (*Table 4*).

While in 1984 conventional angiograms were 'always' required before operation by 72 per cent of surgeons, by 1989 only 23 of 110 (21 per cent) surgeons 'always' required these angiograms. Conversely, no less than 62 (56 per cent) surgeons 'rarely' or 'never' required conventional angiograms before operating. Much preoperative imaging in 1989 was done using digital subtraction angiography; intra-arterial digital subtraction angiography was more popular than intravenous digital subtraction angiography (*Table 5*).

The operation was performed under general anaesthesia by 105 surgeons; two of the remaining five used local anaesthesia 'sometimes', and three of them 'rarely'. There has been no

Table 1 *Numbers of surgeons and carotid endarterectomies performed in 1989*

Frequency of carotid endarterectomy	No. surgeons	No. operations
1–10	67 (56)	309 (240)
11–20	18 (17)	256 (263)
21–30	14 (10)	347 (261)
31–40	5 (5)	169 (176)
41–50	4 (4)	174 (185)
51–60	1 (1)	59 (52)
>60	1 (3)	103 (197)
Total	110 (96)	1417 (1374)

Figures for 1984 in parentheses

Table 2 *Sources of referral to 110 surgeons in 1989*

	Frequency of referral			
Referral source	Often	Sometimes	Rarely	Never
Neurologist	42 (41)	27 (22)	11 (13)	30 (20)
Family doctor	20 (14)	47 (34)	32 (27)	11 (21)
General physician	21 (23)	57 (41)	15 (20)	17 (12)
Ophthalmologist	21 (18)	26 (22)	20 (19)	33 (37)

Figures for 96 surgeons in 1984 in parentheses

Table 3 *Indications for carotid endarterectomy given by 110 surgeons in 1989*

	Operation performed			
Indication	Often	Sometimes	Rarely	Never
Asymptomatic bruit	0 (0)	3 (2)	24 (23)	83 (70)
Transient ischaemic attack	97 (83)	13 (9)	0 (1)	0 (2)
Minor stroke	28 (19)	36 (34)	16 (11)	30 (31)
Stroke	4 (5)	16 (17)	26 (27)	64 (46)

Figures for 95 surgeons in 1984 in parentheses

Table 4 *Screening techniques used by 110 surgeons in 1989*

	Frequency of use			
Technique	Always	Sometimes	Rarely	Never
Duplex scan	54	23	5	28
Intravenous digital subtraction angiography	28	22	10	50
Intra-arterial digital subtraction angiography	22	21	7	60

Table 5 *Use of angiograms by 110 surgeons before operation in 1989*

	Frequency of use			
Angiogram	Always	Often	Rarely	Never
Conventional	23	25	13	49
Intravenous digital subtraction angiography	22	18	12	58
Intra-arterial digital subtraction angiography	26	22	16	46

Table 6 *Type of material used by 110 surgeons for patch closure of carotid arteriotomy*

	Frequency of use			
Patch material	Always	Sometimes	Rarely	Never
Vein	6	26	16	62
Polytetrafluoroethylene	1	5	3	101
Dacron®	1	7	5	97

significant change from the widespread preference for general anaesthesia noted in the 1984 study

The use of a shunt has become more popular since 1984. In 1989, 42 (38 per cent) surgeons 'always' used a shunt, 65 (59 per cent) 'sometimes' or 'rarely' used a shunt, and only three (3 per cent) never used one. The corresponding 1984 figures were respectively: 33 per cent, 51 per cent and 16 per cent. The most popular shunt used by both inveterate and occasional users was the Javid; 27 surgeons always used this shunt and 43 occasionally did so The next popular was the Pruitt shunt, the respective number of users were nine and 26, followed by six and five for users of other types of shunt. Of the 65 occasional users, 43 made their decision to use shunts mainly on 'stump' pressure criteria (generally a systolic pressure of <50 mmHg was thought to require a shunt), seven on electroencephalogram or cerebral monitor change, three on paresis under local anaesthesia, and 12 on other criteria (often these were angiogram appearances indicating contralateral carotid artery disease).

Blocking the carotid sinus nerve with local anaesthetic was done 'always' by 54 (49 per cent) surgeons, 'sometimes' by 15 (14 per cent), 'rarely' by nine (8 per cent), and 'never' by 32 (29 per cent). The corresponding figures for 1984 were 37 per cent, 15 per cent, 11 per cent and 38 per cent respectively, suggesting that nerve blockade has become more fashionable over the past 5 years.

In 1984 the carotid arteriotomy was closed with a patch 'always' by 2 per cent of surgeons, 'sometimes' by 18 per cent, 'rarely' by 22 per cent and 'never' by 58 per cent. By 1989 patch closure was used more often; vein was the most popular material used for the patch (*Table 6*).

Discussion

The referral of patients who might benefit from carotid endarterectomy to surgeons has not changed over the past 5 years; the commonest source is from neurologists. Nevertheless, it is interesting that cardiac surgeons do not make referrals more often and it seems that the need for carotid endarterectomy before or at the time of coronary artery bypass surgery is not perceived as great. Similarly, there has been little change in the indications for carotid endarterectomy, with transient ischaemic attack and stroke resolving within 7 days accounting for nearly all the operations performed in 1989.

Very few surgeons now submit potential candidates for operation directly to angiography and its attendant risks[20,21]. Initial screening with non-invasive (or less invasive) technology is widespread and duplex ultrasonography is the clear leader in this field. No doubt its safety, speed, low cost and reliability have played a part, but it may well be that increasing availability is the major factor and vascular units without this technology should be considered less well equipped[22]. It is probable that most surgeons will accept a technically satisfactory normal duplex scan without recourse to subsequent confirmatory angiography. Intra-arterial digital subtraction angiography and intravenous digital subtraction angiography are being used more frequently, despite their cost and safety disadvantages compared with ultrasonography[21,23]. The main benefit of digital subtraction angiography is its increasing use for definitive imaging before surgery. In this respect, intra-arterial digital subtraction angiography is rather more popular than intravenous digital subtraction angiography which is perhaps not surprising because the latter technique has recently been criticised[21–23] Nevertheless, intravenous digital subtraction angiography is a safe technique and most surgeons find some form of digital subtraction angiography generally reliable, only 21 per cent always require conventional angiography before operating and more than half (56 per cent) rarely or never use conventional angiograms.

The present data have highlighted certain trends in operating technique, with the use of a shunt, blocking of the carotid sinus nerve, and closure of the arteriotomy with a patch all being widely used. Although increasing evidence of a high rate of restenosis after carotid endarterectomy[24,25] makes patch closure more attractive, there is no such obvious reason for the other trends. Perhaps shunt, nerve block and patch closure may be taken together as generally appearing safer than their respective alternatives, and so more appropriate in an increasingly safety-conscious surgical environment, especially when the operation concerned is not free from controversy and is usually prophylactic in nature.

In the USA, the annual frequency of carotid endarterectomy fell from a peak of 465 per million of population in 1985 to 360 in 1986[4]. Although there has been some disaffection with the operation, it is still more widely used than in Great Britain and Ireland, where the annual frequency per million remains between 23 and 24. In 1986 Eastcott[26] stated, 'the broad Atlantic gulf exists; and perhaps somewhere between lies the proper course'. If this is so, on current trends the Americans will reach that 'proper course' before their British and Irish counterparts. Carotid endarterectomy remains unpopular on this side of the Atlantic and it is unlikely that publication of the results of the ageing European Carotid Surgery Trial, now in its ninth year, will alter attitudes dramatically

Perhaps the overall low number of operations persuades surgeons that it is reasonable for individuals to perform only a few carotid endarterectomies per year. Nevertheless, it does seem surprising, following the Confidential Enquiry into Perioperative Deaths[27], that the trend does not reflect a reduction in the number of 'occasional' carotid endarterectomies. The reverse is true: 56 surgeons performed $\leqslant 10$ carotid endarterectomies in 1984, while 67 performed $\leqslant 10$ in 1989; 38 of these 67 surgeons, more than one third of the total, performed $\leqslant 4$ operations in 1989, an experience which others have linked with unfavourable results[17,18]

In conclusion, this survey has shown that the referral pattern and indications for carotid endarterectomy have remained unchanged in Great Britain and Ireland over the past 5 years Major change has occurred in investigation techniques, with an increase in duplex scanning for screening and an increase in digital subtraction angiography (and duplex scanning alone) for definitive imaging before operation Certain surgical techniques have become more popular. shunt usage, nerve block and patch closure. Overall, however, the number of operations performed annually has not significantly changed and carotid endarterectomy continues to be performed by surgeons with widely differing experience of the procedure

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Predictors of death from aortic aneurysm among middle-aged men: the Whitehall study

D. P. Strachan

Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, London, UK

Correspondence to:
Dr D. P Strachan, Department
of Public Health Sciences,
St. George's Hospital Medical
School, Cranmer Terrace, London
SW17 0RE, UK

Among 18 403 male civil servants examined at age 40–64 years there were 99 deaths attributed to aortic aneurysm during 18 years of follow-up. Each case was matched by age to ten controls who survived longer than the case. The risk of all types of fatal aneurysm was substantially increased for current smokers of manufactured cigarettes (rate ratio compared with lifelong non-smokers = 6·5, 95 per cent confidence interval 2·3–18·7), pipe or cigars (6·7; 1·7–26·5) and hand-rolled cigarettes (25·0; 7·5–83·3). Diastolic blood pressure was strongly associated with dissecting aneurysm (rate ratio per 10 mmHg increase = 2·4; 95 per cent confidence interval 1·7–3·2) and abdominal aneurysm (1·5; 1·2–1·9) but not other aneurysms (1·0; 0·7–1·5). The independent effects of height, adiposity, plasma cholesterol, glucose intolerance, reported angina and intermittent claudication were not significant. Hypertension and smoking, particularly of hand-rolled cigarettes, are confirmed as major and potentially remediable risk factors for fatal aortic aneurysm.

Deaths from aortic aneurysm are of current interest because of a recent rise in the incidence of ruptured abdominal aneurysms[1–3] and related mortality[1], and because the advent of abdominal ultrasonography has offered an opportunity for prevention of aneurysm rupture by screening[4].

Prospective epidemiological studies have demonstrated the strong association between cigarette smoking and death from aortic aneurysm[5–7] Longitudinal data on the relationship of aneurysms to other cardiovascular risk factors have not been reported because death from aortic aneurysm is a relatively rare event except in elderly men. The roles of hypertension[8] and blood lipids[9] have been investigated only by case-control studies or by descriptive case series. This paper presents prospective data from a long-term follow-up study of men whose cardiovascular risk factors were measured in middle age

Patients and methods

Study population

The Whitehall study[10] has obtained death certificates for male civil servants who were examined from 1967 to 1969 This analysis is limited to the 18 403 men aged 40–64 years of age at examination, of whom 4189 died on or before 31 January 1987 The underlying cause of death has been coded throughout to the eighth revision of the International Classification of Diseases (ICD8). Deaths attributed to aortic aneurysm (ICD8 codes 441.0–441.9) were subdivided into dissecting aneurysms (441.0), abdominal aneurysms (441.2) and other aneurysms

The examination at entry[10] included measurement of height, weight and triceps skinfold thickness Blood pressure was measured using the London School of Hygiene sphygmomanometer with the subject seated. Subjects attended after an overnight fast and capillary blood samples were collected 2 h after a 50 g oral glucose load for measurement of blood glucose and cholesterol concentrations. Glucose intolerance was defined as a history of diabetes or a postprandial blood glucose level above the 95th centile as described previously[11] Questionnaire information included lifetime smoking habits, employment grade and history of cardiorespiratory symptoms[12]

Statistical analysis

Statistical Analysis System (SAS)[13] was used for data processing and statistical modelling was performed using the Epidemiological Graphics, Estimation and Testing package (EGRET)[14] Analyses were conducted by a 'nested' (within-cohort) case-control approach Cases were defined as men dying from aortic aneurysm during the 18 years of follow-up Ten matched controls for each case were selected at random from men of the same single year of age at entry who survived longer than the case from their date of examination.

The matched case-control sets were analysed by conditional logistic regression. Case-control status was the outcome variable and smoking history and other cardiovascular risk factors were entered as explanatory variables Coefficients from such regression models are equivalent to those obtained by proportional hazards regression[15] and estimate the logarithm of the rate ratio (log relative risk) per unit increase in an explanatory variable.

Results

Cases

In all, 99 deaths were attributed to aortic aneurysm among 18 403 men who each contributed an average of 16·6 years of follow-up. There were 38 deaths with the underlying cause certified as dissecting aneurysm, 41 as abdominal aneurysm, four as thoracic aneurysm and 16 at an unspecified site. There were seven deaths at ages 48–59 years, 22 at ages 60–64 years, 30 at ages 65–69 years and 40 at ages 70–81 years

Smoking

Table 1 shows the distribution of cases by smoking habit and diastolic blood pressure at examination For all types of fatal aneurysm, the rate ratios (relative risks) for smokers relative to lifelong non-smokers, adjusted for diastolic blood pressure, by conditional logistic regression analysis were. 1·3 (95 per cent confidence interval 0·42–4·1) for ex-smokers, 6·5 (2·3–18·7) for current smokers of manufactured cigarettes, 6·7 (1·7–26·5) for smokers of pipe or cigars, and 25·0 (7·5–83·3) for smokers of hand-rolled cigarettes. The difference between the risks for current smokers of manufactured and hand-rolled cigarettes was highly significant ($\chi^2 = 10{\cdot}0$, d.f. = 1). Smokers of manufactured cigarettes who inhaled were at increased risk compared with those who did not (rate ratio = 2·1; 1·0–4·2, $\chi^2 = 4{\cdot}28$, d.f. = 1). Among the smokers of hand-rolled cigarettes there was a similar, but not significant, relationship to smoke inhalation (rate ratio = 2·6; 0·63–10·8). There was no increase in risk with number of cigarettes smoked daily among the current smokers of either manufactured cigarettes or hand-rolled cigarettes.

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Blood pressure

Diastolic blood pressure (phase 4) was found to be a stronger predictor of death from aortic aneurysm than was systolic blood pressure, as judged by the likelihood ratio χ^2 statistics. After controlling for smoking habit, the effect of diastolic pressure adjusted for systolic was significant ($\chi^2=15{\cdot}5$, d.f. = 1), whereas the effect of systolic pressure given diastolic was minimal ($\chi^2=0{\cdot}16$, d.f. = 1).

Table 2 shows the rate ratios for current smokers (by type of tobacco smoked) and for diastolic blood pressure when each type of aneurysm was considered separately In this analysis, the reference group for the smokers was redefined to include both lifelong non-smokers and former smokers, as there were no cases of 'other' aneurysm among those who had never smoked.

The rate ratios for smoking were broadly similar for each type of aneurysm, and the variations across the three causes of death were within the range expected by chance (χ^2 for interaction on 2 d f.: 0·26 for manufactured cigarettes, 1·68 for pipe or cigars, 1·06 for hand-rolled cigarettes). In contrast, the strength of the relationship with diastolic blood pressure varied significantly with, type of aneurysm (χ^2 for interaction = 12·5, d.f. = 2) The association with blood pressure was greatest (and highly significant) for dissecting aneurysm and was absent for 'other' aneurysms. The effect of blood pressure on risk of ruptured abdominal aneurysm was intermediate, but statistically highly significant.

Other cardiovascular risk factors

Table 3 shows the effect of other cardiovascular risk factors on mortality from all types of aortic aneurysm, adding each factor individually to a model containing terms for diastolic blood pressure, and current smoking by type of tobacco smoked and inhalation behaviour. None of the factors reached conventional levels of statistical significance, although the confidence

Table 1 *Number of deaths in the aortic aneurysm and control groups by smoking habit and diastolic blood pressure at entry*

	Diastolic (phase 4) blood pressure (mmHg)				
	<80	80–89	90–99	⩾100	Total
Never smoked					
Dissecting	0	0	1	1	2
Abdominal	0	1	0	1	2
Other	0	0	0	0	0
All cases	0	1	1	2	4
All controls	82	40	24	14	160
Former smoker					
Dissecting	0	0	0	5	5
Abdominal	0	4	3	1	8
Other	1	2	1	0	4
All cases	1	6	4	6	17
All controls	124	134	107	63	428
Current smoker (pipe or cigars only)					
Dissecting	0	0	1	4	5
Abdominal	0	1	0	0	1
Other	0	0	0	0	0
All cases	0	1	1	4	6
All controls	16	18	5	2	41
Current smoker (manufactured cigarettes)					
Dissecting	3	3	4	6	16
Abdominal	6	6	4	8	24
Other	4	3	4	1	12
All cases	13	12	12	15	52
All controls	147	58	65	41	311
Current smoker (hand-rolled cigarettes)					
Dissecting	3	4	1	2	10
Abdominal	1	1	0	4	6
Other	1	1	0	2	4
All cases	5	6	1	8	20
All controls	25	21	4	0	50
Total					
Dissecting	6	7	7	18	38
Abdominal	7	13	7	14	41
Other	6	6	5	3	20
All cases	19	26	19	35	99
All controls	394	271	205	120	990

Table 3 *Mortality ratios for all types of aneurysm related to cardiovascular risk factors*

	Rate ratio	95% confidence interval	Likelihood ratio χ^2 (1 d.f.)
Height (per cm increase)	1·03	(1·00–1·06)	2·62
Body mass index (per kg/m^2)	1·01	(1·00–1·02)	2·41
Triceps skinfold (per cm)	1·01	(0·99–1·03)	1·19
Plasma cholesterol (per mmol/l)	0·96	(0·78–1·18)	0·16
Blood glucose (per mmol/l)	1·07	(0·89–1·27)	0·45
Impaired glucose tolerance (yes *versus* no)	1·3	(0·6–3·0)	0·42
Angina (yes *versus* no)	2·0	(0·9–4·6)	2·35
Intermittent claudication (yes *versus* no)	1·9	(0·6–5·9)	1·13
Employment grade (*versus* administrative, professional and executive grades)			
Clerical	1·0	(0·8–1·3)	1·44 (2 d.f.)
Messenger	1·1	(0·6–2·0)	

Mortality ratios were adjusted by analysis of matched sets using conditional logistic regression

Table 2 *Mutually adjusted mortality ratios for current smokers (relative to current non-smokers) and diastolic blood pressure by type of aneurysm*

	Type of aortic aneurysm			
	Dissecting	Abdominal	Other	All
Diastolic blood pressure (per 10 mmHg increase)	2·4 (1·7–3·2)	1·5 (1·2–1·9)	1·0 (0·7–1·5)	1·6 (1·4–1·9)
Smokers of pipe or cigars only at entry (*versus* non-smokers at entry)	16·7 (3·4–82·1)	2·4 (0·3–22·5)	0·0 (no cases)	5·4 (1·9–15·3)
Smokers of manufactured cigarettes at entry (*versus* non-smokers at entry)	7·7 (2·8–21·7)	4·6 (2·1–10·3)	5·3 (1·7–17·3)	5·3 (3·1–9·1)
Smokers of hand-rolled cigarettes at entry (*versus* non-smokers at entry)	56·5 (13·0–246)	14·6 (4·1–51·7)	33·6 (5·4–210)	20·1 (9·2–43·8)

Values in parentheses are 95% confidence intervals. Mortality ratios were adjusted by analysis of matched sets using conditional logistic regression intervals for dichotomous variables (angina, intermittent claudication, impaired glucose tolerance) were wide and were consistent with large true effects, or none at all The effects of continuous variables such as plasma cholesterol and post-prandial glucose, however, were estimated with precision and found to be minimal. There was little evidence that socioeconomic factors, as reflected by civil service employment grade, were of major importance when smoking habit and blood pressure were controlled in the analysis. Variation in the effect of each risk factor upon specific types of aneurysm was investigated by tests for interaction. These were all not significant at the 10 per cent level.

Discussion

This study is unusual in relating a broad range of cardiovascular risk factors prospectively to mortality from aortic aneurysm. Its main limitations are the use of death certificates rather than clinical or post mortem evidence to identify the cause of death, and the restriction to a middle-aged group among whom the incidence of fatal complications of aortic aneurysms is relatively low. The modest size of the case series may result from under-ascertainment as well as the rarity of the condition. However, it is unlikely that death would be attributed to aneurysm in the absence of some clinical evidence of aortic disease, so most of the certified cases probably were genuine. The validity of the distinction between dissecting, abdominal and 'other' aneurysms is less certain

The findings on smoking confirm those of three large follow-up studies which have demonstrated a strong association between cigarette smoking and death certified as from aortic aneurysm[5–7]. In this study, there was no trend of increasing risk with increasing numbers of cigarettes smoked, in contrast to previous reports. The association with inhalation of smoke, however, would be consistent with such a dose–response relationship. The mortality from aneurysm among ex-smokers was intermediate between that of current smokers and lifelong non-smokers, suggesting that at least part of the risk related to smoking may be reversible on cessation. However, no information was available to assess the effects of changes in smoking habits after the entry examination.

Previous longitudinal studies have not reported on the relationship of smoking to specific types of aneurysm. The findings here suggest a general, rather than site-specific, effect of smoking on the development or rupture of aneurysms. Population surveys[4] and autopsy series[16] have shown a high prevalence of abdominal aneurysms among smokers but smoking has not been reported previously as a factor in the aetiology of dissecting[17,18] or non-dissecting[19] thoracic aneurysms.

Smokers of hand-rolled cigarettes were at higher risk than other smokers of death from all forms of aortic aneurysm. Despite the small numbers of cases, this fourfold difference was unlikely to result from chance and it is rather large to be entirely explained by the effects of bias or confounding among the current smokers. The constituents of tobacco smoke which are responsible for aneurysm formation are unknown, but it may be that they are released in greater quantities from hand-rolled than from manufactured cigarettes. This could usefully be investigated in laboratory and animal studies[20].

The relative risks of death from aneurysm among smokers compared with lifelong non-smokers are intermediate between those for coronary disease and for lung cancer or bronchitis[7] It is likely that the rising incidence and mortality from abdominal aneurysms in England and Wales[1] is mainly a cohort effect attributable to the differential uptake of smoking by successive generations of British men, which was maximal for those born around the turn of the century[21]. This does not exclude the possibility that other factors, such as circulating proteolytic enzymes, copper metabolism or tissue antioxidant levels may determine which smokers develop aneurysmal dilatation rather than atheromatous obstruction[22,23]. Asymmetrical peripheral arterial obstruction in itself may be important in the pathogenesis of abdominal aneurysms[24].

Hypertension is an established risk factor for aneurysm formation, rupture and dissection[4,8,17–19]. Apart from a textual comment that 'the aortic aneurysm death rate of men with a history of high blood pressure was far higher than the rate for men without a history of high blood pressure'[6], this has not been demonstrated hitherto by a prospective study In most subjects, the association of hypertension with aneurysm is likely to be causal, although renal ischaemia secondary to abdominal aneurysm may result in hypertension and, more rarely, untreated coarctation of the aorta may cause both hypertension and aortic dissection[25]. Raised blood pressure may be implicated in the development of atheroma or in the haemodynamic stresses involved in aneurysm rupture or dissection[23]. The latter, at least, are likely to be reversible, and seasonal variation in incidence and mortality from ruptured aortic aneurysm[2] may be attributable to seasonal fluctuations in blood pressure[21].

Aortic dissection is a recognized complication of Marfan's syndrome[17,18] and the non-significant increase in risk of fatal aneurysm with increasing height could reflect vascular changes associated with subclinical Marfan's syndrome[26] However, the correlation with height was not confined to the very tall men, nor to dissecting aneurysms, so this is unlikely to be more than a partial explanation. Plasma cholesterol was not associated with death from any type of aneurysm. This does not, however, exclude a relationship with the ratio of low-density to high-density lipoproteins, as suggested by one case-control study[9].

The major risk factors, hypertension and smoking, are both potentially remediable and are well established targets for primary prevention of coronary and cerebral arterial disease. Recently, there has been increasing interest in the potential for secondary prevention of ruptured abdominal aneurysm by ultrasonographic screening[4]. The same two risk factors, perhaps with family history[27,28], might be considered useful for selecting subgroups of the elderly population at increased risk of abdominal aneurysm or its complications. A history of intermittent claudication has been suggested as a further criterion[29,30]. This did not emerge as an important risk factor in the present study, when the effects of smoking and blood pressure were controlled. However, the prevalence of claudication in middle age is low and different conclusions might apply to a more elderly population.

Three-quarters of the deaths from abdominal aortic aneurysm in this study occurred among 40 per cent of men who were smoking at entry. Although the risk among smokers of hand-rolled cigarettes was exceptionally high, only 15 per cent of the ruptured abdominal aneurysms occurred in this relatively small group (*Table 1*). Among all current smokers, only half of the abdominal aneurysm deaths occurred among the 35 per cent of men with phase 4 diastolic pressures above 90 mmHg at entry. Measurements of blood pressure closer to the time of death might have been more predictive, but these results illustrate the problems of using hypertension as a criterion to select groups for ultrasonographic screening. In any case, the scope for financial savings through excluding low-risk groups is limited because the majority of the expenses (and clinical side-effects) arise not from the screening test itself but from the elective repair of aneurysms detected at screening[31]

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Near-infrared spectroscopy in peripheral vascular disease

T. R. Cheatle,
L. A. Potter*, M. Cope*,
D. T. Delpy*,
P. D. Coleridge Smith
and J. H. Scurr

*Department of Surgery, University College and Middlesex School of Medicine, Middlesex Hospital, London and *Department of Medical Physics and Bioengineering, University College London, London, UK*

Correspondence to:
Mr T. R. Cheatle, Department of Surgery, University College and Middlesex School of Medicine, Middlesex Hospital, Mortimer Street, London W1N 8AA, UK

Near-infrared spectroscopy has been performed on the calf muscles of 38 subjects, 21 normal controls without vascular disease and 17 patients with peripheral vascular disease. Oxygen consumption was measured in the calf by calculating the rate of conversion of oxyhaemoglobin to deoxyhaemoglobin during a period of tourniquet-induced ischaemia. Postischaemic reoxygenation was also measured. Median oxygen consumption in patients with peripheral vascular disease was 0·10 ml 100 g tissue^{-1} min^{-1}, while in the control group it was 0·20 ml 100 g tissue^{-1} min^{-1} ($P<0{\cdot}03$, Mann–Whitney U test). The median time taken to reach maximum oxyhaemoglobin levels after ischaemia was 40 s in patients with peripheral vascular disease and 20 s in controls ($P<0{\cdot}02$). The results indicate that oxygen consumption is reduced in peripheral vascular disease. Near infrared spectroscopy is a non-invasive method for assessing metabolic improvement resulting from surgical or pharmacological treatment.

In 1977, Jobsis discovered that biological tissues possessed a 'window' at near-infrared wavelengths through which light could pass with relative ease[1]. Between the wavelengths 700 and 1300 nm, he found that a detectable amount of light was transmitted across many centimetres of animal tissues *in vivo*. Studying the brain of cats, he further found that only two compounds had absorption spectra in this wavelength range which changed when the inspired oxygen concentration was altered, namely haemoglobin and cytochrome aa_3. By examining the transmission spectrum at a number of different wavelengths and under varying conditions of oxygenation, he was able to calculate changes in the concentrations of oxygenated and deoxygenated haemoglobin (HbO_2 and Hb). Clinical applications of this technique over the past decade have principally been focused on the cerebral circulation. Neonatal cerebral hypoxia and blood flow[2,3], raised intracranial pressure monitoring[4], the effects of gravitational forces on the cerebral oxygenation in fighter pilots[5], and human forearm muscle[6] have all been examined using near-infrared spectroscopy (NIRS). We have applied the technique to the study of calf muscles in patients with peripheral vascular disease.

Animal experiments have indicated that skeletal muscle oxygen consumption (V_{O_2}) is proportional to blood flow[7]. The aim of this study was to ascertain whether V_{O_2} was reduced in patients suffering from intermittent claudication or critical ischaemia, using the non-invasive technique of NIRS. A secondary aim was to observe the rate of increase in concentration of HbO_2 in the leg at the end of a period of ischaemia and relate this to the presence or absence of arterial disease.

Patients and methods

Patients

A group of 38 patients was studied. These comprised 21 subjects without peripheral vascular disease and 17 with claudication or critical ischaemia. The first group was composed of 16 men and five women (mean age 38·0, range 25–82 years) and the second of 13 men and four women (mean age 64·1, range 41–78 years) (*Figure 1*).

All vascular patients underwent segmental Doppler pressure measurements and NIRS performed at the calf. Optodes were positioned on the posterolateral aspect of the calf, midway between the knee joint line and the lateral malleolus. NIRS measurements were collected in the sitting position with the leg extended and supported on a footstool to minimize blood pooling. Measurements were made every 20 s for a resting period of 15 min; a thigh cuff was then inflated to 200 mmHg and spectra continued to be collected every 2 s for the following 3–5 min. The cuff was then released, and measurements made until resting values had been reattained.

Instrumentation

A commercially available near-infrared spectrometer (Hamamatsu Photonics NIR 1000, Japan) was used. Details of the technique as applied to the head of the newborn infant have been described previously[8]. Six semiconductor laser diodes are used as light sources; each produces light at a different wavelength between 770 and 910 nm (*Figure 2*). Individual laser diodes are pulsed sequentially. Light from the diodes is transmitted to the surface of the calf along a fibreoptic cable, the end of which (the optode) is attached to the skin by an adhesive ring. Background light is excluded from the system by a black cloth which is wrapped around the optodes and taped in position. The transmitted light is carried from the other side of the calf along a similar fibreoptic assembly to a photomultiplier tube which counts the emerging photons. (In most cases, the calf muscle proved too thick to measure across its full diameter; in these situations the optodes were positioned between 3 and 5 cm apart.) Transmitted light intensity was measured at all six wavelengths and averaged over a sample time selectable from 2 s upwards. Graphic display of changes in HbO_2 and Hb concentrations could be seen in real time; data were also collected on a computerized data logging system.

Data collection and processing

Quantification of the amounts of HbO_2 and Hb was performed by

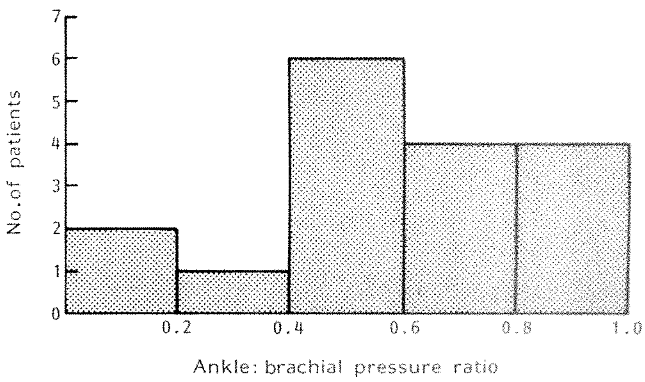

Figure 1 *Ankle:brachial pressure ratios in patients with peripheral vascular disease*

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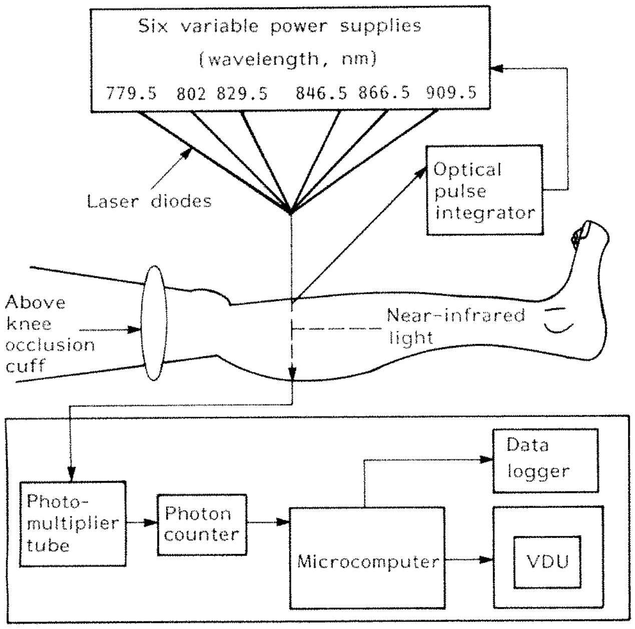

Figure 2 *Near-infrared transillumination and data collection system*

application of the Lambert–Beer law:

$$I = Io\ (10 - ecl)$$

where I and Io represent the intensities of the emergent and incident light respectively, e the specific absorption coefficient for the compound in question, c its concentration and l the optical pathlength of the absorbing solution. The optical pathlength, l, is generally an unknown in scattering media such as human tissue, but a technique has recently been reported which enables the optical pathlength to be approximated according to the formula:

$$l = \mathrm{B}d$$

where B is the 'pathlength factor' for the medium in question and d is the physical distance between the optodes[9]. Once l, e, I and Io are known, then concentrations of HbO_2 and Hb can be quantified. The pathlength factor for neonatal brain has been calculated at 4·39[10]; preliminary work in our laboratory on human forearms has suggested a value of 5·4 for human muscle (unpublished data). We have used this figure in our calculations so that in each case $l = 5.4\ d$. The absorption coefficients used were derived from measurements made on HbO_2 and Hb solutions *in vitro*[11].

Conversion to changes in concentration of HbO_2 and Hb was then performed on a microcomputer by matrix inversion as previously described[11]. This technique assumes that absorption changes due to each compound can be linearly summed; there is evidence of this being an adequate approximation[12]. Changes in concentration were expressed in μmol HbO_2 or Hb l^{-1} min^{-1}. A regression line was then drawn through the declining values of HbO_2 to yield a slope corresponding to the rate of conversion of HbO_2 to Hb. This was converted into the rate of oxygen consumption assuming four molecules of oxygen per molecule of oxyhaemoglobin. A specific gravity of skeletal muscle of 1·06 was taken whenever concentrations were expressed per 100 g tissue. Transformation from μmol O_2 to ml was calculated on the basis of 1 mol O_2 = 22·4 litres O_2.

The times taken for HbO_2 to reach 95 per cent of its peak value following release of the tourniquet were also measured. Statistical analysis was performed using a Mann–Whitney U test to compare groups, as the data were not normally distributed.

Results

Oxygen consumption rates are shown in *Figure 3*. Despite a constant tourniquet pressure of 200 mmHg, with satisfactory abolition of distal pulses both to palpation and pulse oximetry, there was a general tendency for the blood volume between the optodes to increase slightly during the ischaemic period. This was attributed to blood pooling into the venous reservoir of the calf muscles which, if uncorrected, would lead to an erroneously high estimation of oxygen consumption. Therefore calculations were based on observed decreases in the concentration of HbO_2 without reference to Hb, as increases in the latter during the experiment may reflect venous pooling rather than true haemoglobin deoxygenation. In four cases severe alterations in blood volume during ischaemia prevented measurement of oxygen consumption. All four were normal controls.

There was a significant difference in resting oxygen consumption between claudicants (median V_{O_2} = 0·10 ml 100 g^{-1} min^{-1}, interquartile range = 0·04–0·16) and normal subjects (median V_{O_2} = 0·20 ml 100 g^{-1} min^{-1}, interquartile range = 0·16–0·24) ($P < 0{\cdot}03$). However, there was broad overlap between the two groups. Correlation between oxygen consumption values and ankle:brachial pressure ratios was significant at the 5 per cent level but no more; as pressure indices are an imperfect parameter for assessing the severity of peripheral vascular disease the importance of this is uncertain.

Median time taken to reach 95 per cent maximum HbO_2 levels was 40 s (interquartile range = 26–122) in the disease group and 20 s (interquartile range = 13–36) in normals ($P < 0{\cdot}02$). Again, there was broad overlap between the disease and control groups (*Figure 4*).

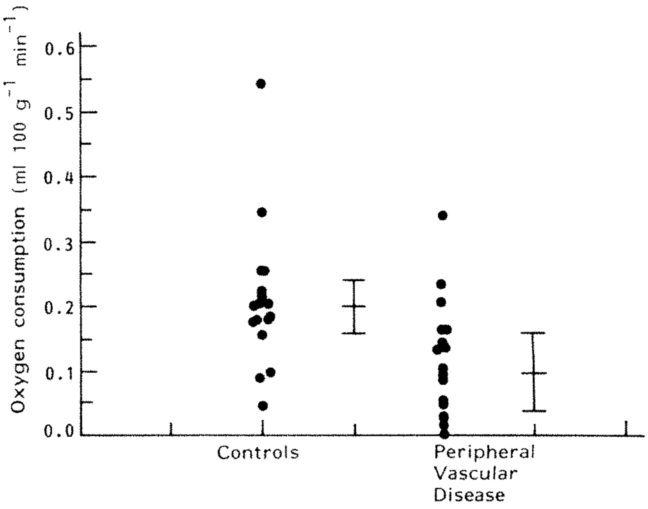

Figure 3 *Oxygen consumption in the calf muscles of patients with and without arterial disease. Descriptors are medians plus interquartile ranges*

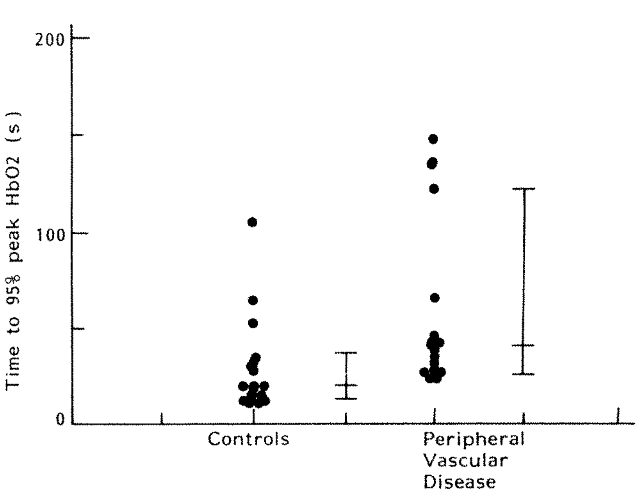

Figure 4 *Time taken to reach 95 per cent of peak oxyhaemoglobin level at the end of a period of arterial occlusion. Descriptors are medians plus interquartile ranges*

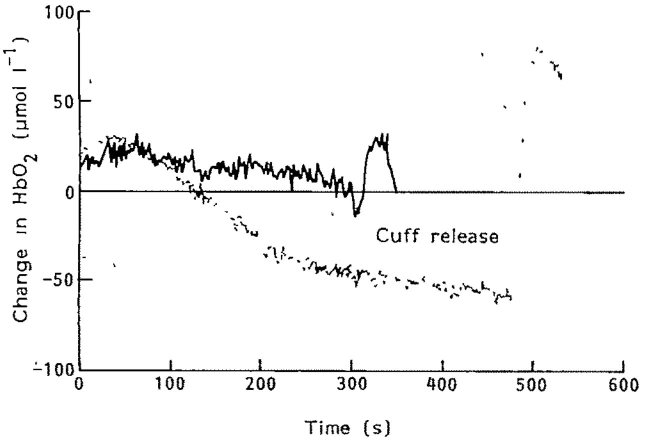

Figure 5 *Examples of haemoglobin deoxygenation slopes obtained from a normal control and from a severe claudicant during arterial occlusion.* ——, *Claudicant*, -----, *normal*

The greater rate of O_2 consumption in healthy limbs is indicated by a comparison of the slopes shown in *Figure 5*. The lower, steeper slope depicts the rate of haemoglobin deoxygenation in a healthy 30-year-old non-smoking woman during a period of arterial occlusion. The oxygen consumption was calculated as 0·186 ml 100 g $tissue^{-1}$ min^{-1}. The rate of deoxygenation slowed considerably after ischaemia for approximately 3 min. This may be ascribed to a change from haemoglobin deoxygenation to myoglobin deoxygenation. The rapid rise in haemoglobin oxygenation on the right of the graph represents arterial blood inflow after release of the occlusion cuff.

The upper slope, by contrast, shows the much slower rate of oxygen utilization in the leg of a 71-year-old man with a claudication distance of 50 m and a maximum walking distance of 70 m. His ankle brachial pressure index was 0·55. The oxygen consumption was 0·031 ml 100 g $tissue^{-1}$ min^{-1} In addition to the slow rate of haemoglobin deoxygenation, it is clear that the rate of inflow of oxygenated blood following cuff release is substantially slower than that in the healthy limb.

Discussion

The potential importance of this new technique lies in the fact that it assesses the effect of ischaemia on the end-tissues rather than merely documenting the degree of reduction of blood flow. That there may be a discrepancy between the degree of ischaemia in a limb and the resultant tissue damage is now well recognized For example, Doppler ankle artery pressure measurements correlate poorly with the healing or otherwise of forefoot amputations performed for peripheral vascular disease[13]. Transcutaneous oxygen measurements are a better predictor of amputation healing[14] but these do not examine the effect of ischaemia on muscle, which causes most patients their principal symptoms. Treadmill testing is at least related to symptoms arising from the calf muscles but is by its nature subjective and poorly reproducible[15]; in addition, different protocols between centres prevent comparison of patient groups. Recent advances in the investigation of peripheral arterial occlusive disease, such as the measurement of pulse-generated runoff to determine calf vessel patency[16] and the use of radioisotopes to measure limb blood flow[17], do not yield metabolic information.

The investigation of human muscle metabolism *in vivo* is in its infancy. Arterial and venous blood gas analysis will indicate the overall oxygen consumption of the limb, but are not tissue-specific Indirect assessment of oxygen consumption can be made by examining the effect of ischaemia on tissue levels of phosphocreatine. Nuclear magnetic resonance spectroscopy has demonstrated the greater depletion of phosphocreatine that occurs during exercise in claudicants[18] but this cannot reveal metabolic abnormalities at rest and is, in addition, a complex and expensive investigation unsuited to everyday use.

Near-infrared spectroscopy has been shown to be a potentially valuable indicator of oxygen delivery and utilization in healthy muscle. In a study on the forearms of ten healthy young adults, Hampson and Piantadosi demonstrated that the technique was significantly more sensitive in indicating tissue oxygen availability than transcutaneous oximetry[6]. They found that arterial occlusion led to a rapid depletion of muscle oxygen stores over a period of 4–6 min; these findings correlate well with the present results.

The finding of a median V_{O_2} of 0·19 ml 100 g^{-1} min^{-1} in normal subjects is comparable to those reported in animal studies[7,19,20]. That it is slightly lower than in most of the animal work may be explicable in terms of interspecies differences, as smaller mammals generally have a higher basal metabolic rate than larger ones. In a study on the forearms of 16 healthy young adult volunteers, Mottram found values for muscle V_{O_2} to average 0·24 ml 100 g^{-1} min^{-1} (Ref. 21) He also reviewed four previous reports on human muscle metabolism at rest All resulted in estimations of muscle V_{O_2} of between 0·12 and 0·18 ml 100 g^{-1} min^{-1}, very similar to the present results.

Our technique for measuring oxygen consumption involves making certain assumptions Myoglobin has identical absorption spectra to haemoglobin[22] and the two species cannot be separated by NIRS. However, in animal experiments involving exchange transfusion, Seiyama *et al.* found that myoglobin contributed less than 10 per cent to the NIRS signal in skeletal muscle[23]. A second assumption has been that skin and subcutaneous fat contribute a negligible amount to the amount of oxygen being consumed, based on the work of Piantodosi *et al.*[22] who showed that double thickness skin folds contributed less than 5 per cent to the NIRS signal of transilluminated human forearm.

Since the technique of NIRS involves measuring haemoglobin oxygenation rather than oxygen itself, it is not possible to take into account oxygen in solution. This may lead to an underestimation of V_{O_2}, since dissolved oxygen will act as a reservoir by which deoxygenated haemoglobin can become reoxygenated; this will not be reflected in NIRS data However, as the proportion of oxygen in solution in blood is usually less than 2 per cent of the total[24], the resultant error is likely to be minimal.

One criticism of the study could be the age discrepancy between the disease and control groups. However, analysis of those control subjects aged over 45 years shows a median oxygen consumption of 0·19 ml 100 g^{-1} min^{-1}, compared with an overall control median of 0·20 ml 100 g^{-1} min^{-1} The difference between the groups is, therefore, not simply a function of age.

The mechanism which leads to patients with severe claudication having a lower rate of oxygen consumption than normal is unclear. Loss of 'vasomotion' (the regular opening and shutting of capillary loops) has been convincingly demonstrated in arterial disease by Fagrell and colleagues using laser Doppler velocimetry[25], and this may lead to more 'capillarons' (a capillary and the tissue it perfuses) being without blood flow at any one time. Evidence indicates that mitochondrial oxidative capacity increases adaptively in intermittent claudication[26,27]. However, mitochondrial oxygen consumption is directly dependent on substrate availability[28], and the reduced oxygen consumption seen in the present study may be due to a reduction in available high energy compounds, such as phosphocreatine.

We would not suggest that the technique is an appropriate tool for the diagnosis of peripheral vascular disease, as the overlap between the groups in oxygen consumption rates is significant. Although the rate of HbO_2 increase after ischaemia correlates well with severity of disease, there are more readily available ways of assessing blood flow in clinical practice. However, it is likely that NIRS will facilitate the objective assessment of response to drug treatment. As we approach the limits of what is technically feasible in the field of surgical reconstruction, the importance of effective pharmacotherapy will increase The demonstration of objective improvement in muscle tissue function by a repeatable technique will play an important role in the evaluation of new drugs. NIRS is well suited to this purpose. It may be an appropriate tool to use in assessing the effect of surgical reconstruction on muscle perfusion, and can also be expected to contribute in metabolic terms to our understanding of what constitutes 'critical ischaemia'.

The prototype Hamamatsu NIR 1000 instrument used in this study is a complex research instrument. The technique of NIRS is becoming of recognized clinical value in the field of monitoring neonatal cerebral hypoxia, and may do so in the assessment and monitoring of peripheral vascular disease. With the advent of larger scale production, simpler low-cost instruments aimed more at clinical than research use are likely to become available, making this a convenient and easily repeatable technique for assesssing muscle metabolism in patients with arterial disease.

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Results of a recently instituted programme of thrombolytic therapy in acute lower limb ischaemia

K. J. Dawson, K. Reddy*, A. D. Platts* and G. Hamilton

Departments of Surgery and
**Radiology, Royal Free Hospital*
and School of Medicine,
Pond Street, Hampstead, London
NW3 2QG, UK
Correspondence to:
Mr G. Hamilton

Twenty-eight patients with acute lower limb ischaemia received low dose intra-arterial thrombolytic therapy over a 2-year period. Eighteen patients received streptokinase and ten patients received recombinant tissue plasminogen activator (rTPA). Indications included arterial thromboemboli and graft failures. Mean ischaemic times were similar in both groups. Treatment time to achieve lysis was significantly less with rTPA ($P<0{\cdot}01$)*. Subsequent vascular procedures, including angioplasty or reconstruction, were undertaken in 36 per cent of patients. Arterial puncture site bleeding occurred in eight (29 per cent) patients. Three (11 per cent) patients suffered rethrombosis after initial successful lysis. All rethromboses were successfully lysed with rTPA. There were two major amputations. Five (18 per cent) patients died, all lytic failures in the streptokinase treatment group. There were no cerebral haemorrhagic events and no patient died as a result of thrombolytic therapy. Good clinical outcome was obtained in nine of 18 patients treated with streptokinase and in nine of ten patients treated with rTPA. Intra-arterial thrombolysis provides effective therapy with high rates of limb salvage and a low mortality rate. This study suggests that rTPA may be a more effective agent, causing less morbidity, than streptokinase.*

Plasminogen, formed in the liver, circulates in plasma and becomes bound to the surface of a thrombus. In the normal physiological situation tissue plasminogen activator is released in minute amounts from the vascular endothelium and preferentially acts on thrombus-bound plasminogen, cleaving it to plasmin[1,2]. This active fragment then digests the fibrin portion of a clot, breaking it down into the products of clot lysis. All known thrombolytic agents, including streptokinase, work indirectly via activation of plasminogen[3]. Tissue plasminogen activator is unique in that its action is specific to thrombus. Although streptokinase is a cheap and effective agent with a proven therapeutic record[4], it does not share the thrombus specificity of tissue plasminogen activator and has a significant spill-over effect on the systemic haemostatic system. This lack of local specificity is one of its main disadvantages. Attempts to improve thrombus specificity led to the successful isolation and cloning of human tissue plasminogen activator (rTPA) in 1983[5]. Using recombinant-DNA techniques, the human genome has been inserted into a non-malignant mammalian cell line, thus producing commercial quantities of the substance for therapeutic use.

In the late 1980s there have been several reported series of its use in peripheral arterial disease, mainly from the USA[6-9], but increasingly from the UK[10,11]. Dose-ranging studies from the UK have established a safe and effective low dose regimen[12]. All series reported have consistently indicated that rTPA is superior to other commonly used agents and this is broadly in agreement with the literature reported for coronary artery thrombolysis[13].

Patients and methods

Over a 2-year period from October 1987 a total of 28 patients were treated by thrombolysis. There were 19 men and nine women. Eighteen patients were treated with low dose intra-arterial streptokinase and ten with low dose rTPA. The age range was 40-95 years with a mean(s.d.) of 69·3(13·9) years. There was no significant difference in age between the sexes or treatment groups (Mann-Whitney *U* test).

Patients excluded were those with a clinically obvious embolus of <48 h duration and those in whom immediate revascularization was indicated because of the presence of paraesthesia and paralysis. These were treated by emergency embolectomy or reconstruction.

Retrospective analysis, using clinical criteria, identified four main groups of patients. In the first group, three patients had emboli. Two of these were patients with uncontrolled atrial fibrillation presenting with occlusions of >1 week in duration and the third patient had calf and foot vessel occlusion with an ipsilateral popliteal aneurysm. In the second group, three patients presented within 12 h of cardiac catheterization. These were probably embolic in nature or secondary to catheter trauma, but at least one may have been thrombosis following hypotension. In the third group, seven patients suffered failure of femoropoliteal grafts, comprising two Dacron® (E.I. du Pont de Nemours, Wilmington, Delaware, USA), two Gore-tex® (W.L. Gore, Woking, UK) and three autogenous vein grafts. A fourth group of 15 patients was felt to have had acute thrombosis in arteries already diseased by atheroma.

All diagnostic angiography was performed in the radiology department; serial digital subtraction angiography was performed at intervals of about 12 h to assess lysis, using a dedicated Elscint Eclat (Elscint (GB) Ltd., Watford, UK) digital subtraction unit with a 12 inch (30 cm) image intensifier. Sequential overlapping runs at a framing rate of one image per second were used to demonstrate the arterial system following injections of 20 ml Iohexol 240 (Nycomed (UK) Ltd., Birmingham, UK) at a rate of 10 ml/s via a 5 Fr pigtail catheter (Cordis (UK) Ltd., Brentford, UK), inserted whenever possible through the contralateral groin. This was then exchanged for a 5 Fr Sidewinder II (Cordis) through a 7 Fr introducer sheath (Cordis). This catheter was then impacted in the proximal part of the thrombus which was gently dissected with a guide-wire and the infusion begun. At the end of infusion if any lesion suitable for balloon dilatation was found, angioplasty was performed as soon as possible. If cross-over of the aortic bifurcation failed or was anticipated to be difficult, ipsilateral antegrade catheterization was performed. There was a change in angiographic technique for the last ten patients treated. In these cases, the catheter introducer sheath was not removed but left *in situ* in the vessel. All subsequent catheter manipulations and catheter changes were carried out via this sheath. This decreased vessel trauma and so reduced groin bleeding. Thrombolytic agents were also infused into the side port of this sheath around the catheter to prevent pericatheter thrombus (*Figure 1*). A further advantage of this technique was that

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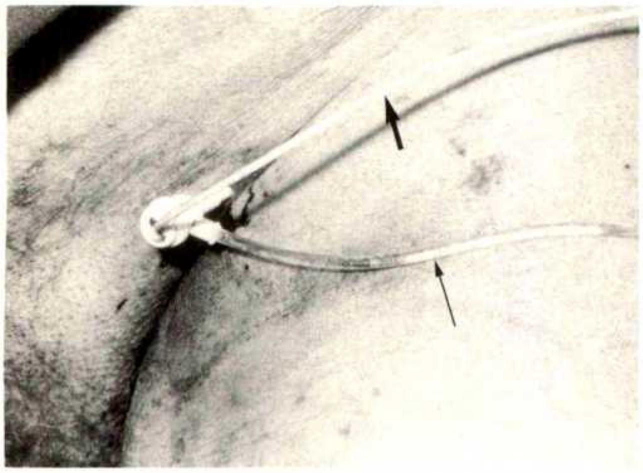

Figure 1 *Infusion via angiography catheter (thick arrow). Thin arrow shows side port of catheter sheath*

any angioplasties required could be done through the sheath without further puncture of the vessel. All patients having streptokinase infusions received 5000 units plus 250 units heparin per hour in a saline infusion. All patients having rTPA received 0·5–1·0 mg plus 250 units heparin per hour in a saline infusion, although latterly the use of heparin has been discontinued as it may interfere with the action of rTPA[11].

No patient was anticoagulated following successful thrombolysis but all received antiplatelet therapy (75 mg/day aspirin). Two patients were treated within 10 days of surgery for failed embolectomy and thrombosis of a recent femoropopliteal graft, respectively. The former had successful lysis without major complication and the latter was anticoagulated following unsuccessful treatment of the graft thrombosis.

Results

Ischaemic time ranged from 6 to 21 days in the streptokinase group with a mean of 7·6 days and a median of 5·5 days. In the rTPA group, the occlusions ranged from 12 h to 84 days, with a mean of 18·5 days and a median of 10·5 days. Several particularly lengthy occlusions in the rTPA group have skewed the mean occlusion time but there is no significant difference in this respect between the two treatment groups (Mann–Whitney *U* test). The mean(s.d.) infusion time required to achieve lysis with streptokinase was 54·0(28·3) h. With rTPA, the mean(s.d.) was 32·7(11·9) h which was significantly shorter (Mann–Whitney *U* test, $P < 0{\cdot}01$).

The results were analysed separately for graft failures and for arterial occlusions. There were 21 arterial occlusions, 13 of which had complete lysis shown by angiography and which produced an excellent clinical result. There was no improvement in eight patients of whom five died and three required arterial reconstruction. Of the seven graft failures, five showed complete lysis on an angiogram with an excellent clinical result. The two patients who did not improve were treated respectively by femoropopliteal reconstruction and by anticoagulation after an attempt at reconstruction was deemed unsuitable. Both failures were in autogenous vein grafts with occlusions of 8 and 11 days respectively. The single vein graft successfully lysed had been occluded for only 12 h. Lysis in the two Gore-tex and two Dacron grafts produced excellent angiographic and clinical results. Three patients had rTPA infusions increased to a maximum of 2·0 mg/h when no lysis was evident on the initial check angiogram. These three patients had complete lysis following increased dosage.

Good results were obtained in nine of 18 streptokinase and in nine of ten rTPA-treated patients (*Table 1*).

Subsequent procedures were performed on ten patients: angioplasty (four cases), angioplasty and graft (one case), femoropopliteal graft (three cases), femorofemoral graft (one case), and aortofemoral plus femoropopliteal graft (one case). The figure of 36 per cent (ten of 28) is somewhat lower than those found in other reports but it is probably accounted for by several factors. Six (21 per cent) of 28 patients did not have diseased arteries but had occlusion secondary to either emboli or cardiac catheterization. Because of their more normal vessels these patients would not have the same requirement for subsequent angioplasty. There is no matching between the various studies reported with regard to anatomical extent or duration of occlusion, or with the degree of initial ischaemia, factors which influence the frequency of subsequent procedures and which may account for the differences in reported follow-up procedures between different centres.

Surgical intervention for bleeding was not required. Complications were mainly minor but included haematoma (7 groin, 1 calf), rethrombosis (3) and amputation (3 minor, 2 major). There were 16 complications in 13 patients (ten received streptokinase and three received rTPA) who had a mean thrombolytic infusion of 56·6(25·3) h. No complications were recorded in 15 patients who had a mean infusion of 45·0(27·9) h. Complications were not significantly associated with longer infusions (Mann–Whitney *U* test).

The three minor amputations comprised two autoamputations of toes and one forefoot amputation. All three patients had initially presented with gangrene in these areas. There were two major amputations: one below-knee amputation in a patient who later died and one above-knee amputation.

The three cases of rethrombosis all occurred within weeks of initial clearance and were all successfully lysed with rTPA. Two of these patients had excellent long-term results and one had an above-knee amputation as already described.

Five patients died. All were lytic failures in the streptokinase treatment group and tended to be both older (74·8 years) and to have been ischaemic for longer periods (10·3 days), although these were not significant (Mann–Whitney *U* test).

Discussion

Thrombolysis in the treatment of acute arterial occlusions of the lower limb has been increasingly used since the early 1980s when large series began to be reported[14]. It broadens the therapeutic options available to clinicians dealing with acute occlusions. Many patients may be unsuitable for treatment by conventional embolectomy or be unfit for reconstruction. The use of embolectomy catheters, particularly in atheromatous vessels, can traumatize the endothelium and frequently may worsen the situation. Indeed, the use of embolectomy catheters has been shown to be a reproducible experimental method for inducing endothelial damage and luminal narrowing in animals and to be associated with a high incidence of subsequent vessel stenosis in humans[15,16].

Many occlusions are caused by a single underlying stenosis and when thrombolysis is complete this is revealed allowing simple angioplasty to reverse the lesion. Surgery is often not required. Should surgery become necessary, however, its use is not prejudiced by having attempted thrombolysis first, although the reverse is not necessarily true and thrombolysis should be undertaken with considerable caution following a recent

Table 1 *Outcome after thrombolysis in 28 patients*

	No. of patients		
	Streptokinase	rTPA	Total
Good outcome	9	9	18 (64)
Failure requiring reconstruction	3	1	4 (14)
Failure requiring anticoagulation	1	–	1 (4)
Death	5	–	5 (18)

Values in parentheses are percentages; rTPA, recombinant plasminogen activator arteriotomy. Subsequent surgery, particularly amputation, may be less extensive if inaccessible calf vessel thrombi have been lysed thus improving run-off Forefoot or local amputations often suffice where previously a below-knee amputation may have been required and there is less often need to resort to above-knee amputation. A high proportion of grafts, both synthetic and vein, can be saved and we consider this to be one of the most useful applications of this form of therapy. Vein grafts, particularly when reversed, lose the intimal blood supply derived from their lumen when they thrombose. They are therefore difficult to salvage unless treated early, as evidenced by the two graft treatment failures encountered in the present series.

The mean infusion time was longer for rTPA than in most series from the USA[6,8,9] in which higher doses were used, but was similar to infusion times reported from the UK using the same dose[11]. The infusion time with streptokinase was also longer than some other studies[4]. We preferred to have angiography done by the regular vascular radiologist during office hours to optimize results. This often meant an infusion running overnight, when clinical clearance had already occurred, to maintain patency until check angiography first thing the following morning. We found this routine convenient and it resulted in better quality films. Such a policy increases mean infusion time and this deserves comment. Higher complication rates and longer infusion times have been directly related in that they tend to occur in cases in which there have been prolonged and unsuccessful attempts at lysis. While our policy results in longer infusion times it is not associated with high failure rates. There was no significant difference in the present series between infusion times for complicated or uncomplicated cases. It is the failure of treatment to achieve successful lysis rather than the duration of the infusion which is important. Many preventable complications result from a policy of high dose thrombolysis in an attempt to obtain rapid clearance, an approach which results in a high incidence of bleeding complications. Limbs so threatened as to require speedy revascularization are probably unsuitable for thrombolysis and should be treated by other means. In our experience very few patients fall into this category.

The incidence of groin haematoma has been reduced since changing to rTPA and leaving the angiography sheath in place. While fear of possible bleeding complications has probably prevented more widespread application of thrombolytic techniques in the UK, we believe that the combination of rTPA and the angiographic technique outlined above have controlled this problem. Bleeding should now rarely be a deciding factor in stopping treatment and concern over such a complication should not discourage clinicians interested in initiating thrombolytic programmes

The three cases of rethrombosis successfully cleared with rTPA demonstrate one of the advantages of this agent Owing to possible allergic complications rethrombosis cannot be treated again within 6–12 months with streptokinase and, unless another thrombolytic agent is used, surgical intervention is necessary. This is not the case with rTPA which may be used on multiple occasions in the same patient regardless of time interval, a major advantage.

Limb salvage in this study occurred in 22 of the 23 (96 per cent) survivors Allowing for amputation in a patient who died with a gangrenous leg, the overall limb salvage rate was 87 per cent This compares favourably with other reports of thrombolysis and with reported series of acute embolectomy and reconstruction[17–19], where amputation rates of over 20 per cent are common.

The mortality rate of 18 per cent is also favourable in the context of results of conventional surgical treatment in this elderly age group, for whom mortality rates of over 20 per cent would not be surprising[17]. Some of the best results have occurred with occlusions of over 6 weeks' duration and one patient with an occlusion which was reliably present for over 80 days was successfully treated. The upper limits for ischaemic time suitable for thrombolysis have yet to be defined; an attempt at thrombolysis may be worthwhile in many more cases than previously appreciated.

The place of thrombolysis in the management of acute vascular ischaemia remains to be defined. There have been no proper randomized, prospective trials of thrombolytic therapy reported, either between the available agents or between thrombolysis and surgery. Adequate statistical analysis will require very careful matching of treatment groups and a multicentre study would be needed to recruit sufficient numbers to achieve this For this reason reports from single centres are unlikely to provide definitive, statistically valid results However, our initial experience in a single centre has provided valuable information on the application and development of this technique. As a result we believe that any group with access to 24-h angiographic facilities and dealing with acute arterial occlusions should and can institute a programme of intra-arterial thrombolysis with success.

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Prevention of perioperative deep vein thrombosis in general surgery: a multicentre double blind study comparing two doses of Logiparin and standard heparin

A. Liezorovicz,
H. Picolet,
J. C. Peyrieux,
J. P. Boissel and the
H.B.P.M. Research
Group

Correspondence to:
Dr Alain Leizorovicz, Hôpital
Neuro-Cardiologique, Unité de
Pharmacologie Clinique,
Départment Méthodologie et
essais Therapeutiques, 162 avenue
Lacassagne, 69424 Lyon Cedex
03, France

A total of 1290 patients were enrolled in a randomized multicentre double blind study in order to investigate the use of two doses of a new low molecular weight heparin, Logiparin®, in the prevention of deep vein thrombosis (DVT) in general surgery. Patients who were included had no contraindication to heparin therapy and had at least one of the recognized risk factors for DVT. Patients were randomized to receive unfractionated heparin (UH) 5000 units b.d., Logiparin 2500 units daily or Logiparin 3500 units daily. Each treatment was given subcutaneously 2 h before surgery and continued for 7–10 days. Daily ^{125}I-labelled fibrinogen uptake tests (FUTs) were performed from day 2 to day 7 to detect DVT, and phleboangiography was used to confirm the diagnosis. The wound was examined on a daily basis to check for haematoma formation, and all patients were followed up for 1 month after operation. All three treatment arms were well matched for age, sex, weight, diagnosis and type of operation performed. The three major inclusion criteria in the trial were malignancy, age over 60 years and a history of varicose veins. Positive FUTs (UH = 4·2 per cent, Logiparin 2500 units daily = 7·9 per cent, Logiparin 3500 units daily = 3·7 per cent) and positive angiograms (UH = 3·0 per cent, Logiparin 2500 units daily = 5·6 per cent, Logiparin 3500 units daily = 2·3 per cent) were significantly more common in the Logiparin 2500 units daily group than in the UH and Logiparin 3500 units daily groups. The rates of major complications (severe haemorrhage, death, pulmonary embolism, reintervention) were similar in the three groups.

The value of low-dose heparin (5000 units b.i.d. or t.i.d.) for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism in general surgical patients has been extensively evaluated. A recent overview has confirmed the efficacy of such a treatment which typically reduced the risk of DVT from 22·4 per cent to 9 per cent and of pulmonary embolism from 3 per cent to 1·7 per cent[1].

In the past few years new molecules of heparin with low molecular weight have been introduced. These have interesting new biological properties and they have been alleged in practice to be superior to standard heparin (UH). Several compounds have been developed and have been or are currently being evaluated in patients[2–8]. An investigation was undertaken to assess the prophylactic value on DVT of a new low-dose low molecular weight heparin, Logiparin®, Novo Nordisk, Copenhagen, Denmark as compared with a standard heparin regimen in middle/high risk patients undergoing major general surgery. In addition, since a major problem in clinical trials with low molecular weight heparin is the choice of dose because no biological test allows a truly reliable indicator of its antithrombotic action, two doses of Logiparin were compared concomitantly with UH. The protocol was accepted by the Université Claude Bernard Ethical Committee.

Patients and methods

Patient selection

Between June 1987 and November 1988, patients were recruited from 23 centres located both in France and in the UK. Patients undergoing general surgery (abdominal, gynaecological, urological or thoracic but not cardiac surgery) who were 40 years or older and in whom general anaesthesia longer than 30 min was anticipated were selected. Informed consent was obtained in all cases. Only patients with at least one of the following risk factors for thromboembolic disease were included in the trial: previous history of venous thromboembolism, varicose veins, obesity (overweight >20 per cent), contraceptive pill or hormonal replacement therapy, chronic respiratory insufficiency, heart failure, malignancy, previous long bone fracture of lower limb, bed rest >5 days before surgery, predicted duration of surgery >4 h, age ≥60 years.

Study treatments

There were three treatment regimens in the trial. Logiparin 2500 units once a day (the preparations contained 8333 anti Xa units/ml), Logiparin 3500 units once a day (the preparations contained 11 667 anti Xa units/ml), and Heparin Novo 5000 units b.d. (sodium heparin prepared from hog intestinal mucosa). As Logiparin was given only once daily a second injection was given daily (0·9 per cent NaCl) to ensure that all three regimens were 'blind'. Two hours before surgical intervention patients received a morning injection of the allocated treatment. The second injection was given 12 h later as an evening injection, and injections then followed every 12 h. All treatments were administered by subcutaneous injection. Treatment was continued for at least 7 days and for a maximum of 10 days. If thromboembolic prophylaxis was required for more than 10 days, UH was used according to usual clinical practice. Premature discontinuation of the study treatment was considered as a critical event and documented accordingly. Stockings or other forms of DVT prophylaxis were not allowed during the study period.

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Table 1 *Main baseline characteristics*

	Standard heparin ($n=429$)	Logiparin 2500 units daily ($n=431$)	Logiparin 3500 units daily ($n=430$)
Risk factors			
Previous history of venous thromboembolism	10·9	10·0	11·7
Deep venous thrombosis	76·2	85·0	73·9
Pulmonary embolism	19·1	10·0	13·0
Both	4·8	5·0	13·0
Varicose veins	53·5	44·3	46·2
Obesity (overweight >20%)	29·2	28·9	26·4
Contraceptive pills (current)	1·5	1·0	1·0
Hormonal therapy (current)	3·0	3·0	1·5
Chronic respiratory insufficiency	8·9	10·5	9·1
Heart failure	2·5	3·0	4·1
Malignancy	38·6	39·3	37·6
Previous long bone fracture of lower limb	4·5	4·5	1·5
Bed rest before surgery >5 days	9·9	9·5	5·6
Expected duration of surgery >4 h	9·4	16·9	13·2
Age ≥60 years	56·4	55·2	58·4
Number of risk factors			
1	29·2	29·9	31·5
2	33·2	32·8	38·1
3	21·8	22·9	18·3
4	12·4	11·0	8·1
5	3·0	3·0	3·1
6	0·5	0·5	1·0
Mean per patient	2·3	2·3	2·2
Type of planned surgery			
Abdominal ($n=921$)	71·1 (305)	72·6 (313)	70·5 (303)
Gynaecological ($n=174$)	12·1 (52)	13·9 (60)	14·4 (62)
Urological ($n=127$)	11·2 (48)	9·3 (40)	9·1 (39)
Thoracic ($n=68$)	5·6 (24)	4·2 (18)	6·0 (26)

Values are percentages; values in parentheses are numbers of patients

Study design

A randomized double blind trial was organized by a Coordinating Centre, a Steering Committee, a Critical Event Committee (which assessed major events) and an Executive Committee (operational arm of the Steering Committee).

After baseline examination and assessment of eligibility, the investigator transmitted a request for allocation by computer network to the Coordinating Centre. After checking eligibility the computer program allocated a treatment number corresponding to a treatment box containing the pre-allotted treatment.

Clinical examination was performed before inclusion, on day 8 after operation or at discharge, and 1 month later for evaluation of end-points. Data collected (except documentation of critical events) were circulated through a computer network. The advantages of such a data system were absence of time lag due to mail and central key processes, and on-line editing and correction.

Evaluation of end-points and clinical follow-up

A fibrinogen uptake test (FUT) was performed daily from day 2 to day 7 or 8. On Sundays and holidays the scan was performed only if a positive test was observed on the previous day; there should not have been more than 1 day missing in a series of scans for a given patient and the series should have contained at least six tests if none was positive.

Two criteria were necessary for a positive scan: 20 per cent relative increase between one point and the highest adjacent point or the contralateral point, and persistence of increase on the next day. Assessment of FUT was first done locally after which data from all positive tests were reviewed centrally by a panel of four experts who were unaware of the treatment each patient had received. If a FUT was locally considered positive, phlebography was performed within 36 h of the test.

All angiograms were reviewed centrally by two independent radiologists and the site of DVT, if present, was documented. The protocol specified that venous thrombosis confirmed by angiography was the primary end-point.

Biological data

Blood samples were drawn 24 h before surgery (before the first study treatment injection) and on day 3, day 5 and the day of discharge (but not later than day 10). Red blood cell counts, platelet counts, haematocrit, haemoglobin, activated partial thromboplastin time, prothrombin time and leucocyte counts were performed at each centre. Factor Xa inhibitory (XaI) activity was determined by an automated chromogenic kinetic method at a central laboratory.

Sample size

The total sample size was computed with the assumption of reduction in the incidence of venous thrombosis from 8 per cent (UH) to 2·5 per cent (low molecular weight heparin group), as observed in a previous study[2], with type I error $=0·05$ and type II $=0·05$.

Statistical analysis

Analysis was first carried out on all randomized patients, including patients who did not receive any study medication, in order to evaluate DVT as well as other end-points with the available information. Another analysis was performed on the group of patients who received at least one treatment injection. Univariate analyses were performed using the classical statistical tests (Student's *t* test or analysis of variance, as appropriate).

Results

Patients

Study population. A total of 1290 patients were randomly allocated to receive either SH (429 patients), Logiparin 2500 units daily (431 patients) or Logiparin 3500 units daily (430 patients). Clinical and biological baseline characteristics were fairly well balanced between the three groups; 45 baseline characteristics were compared and no biological or clinical comparison reached $P=0·05$ level. There were 513 men and 777 women and the mean age was 61 years (*Table 1*). The mean number of risk factors for each patient at entry to the study was 2·3.

Protocol deviations. Twenty-seven patients did not have any FUT. Surgery was cancelled in seven and FUTs were not performed in a further 20 (SH, $n=8$; Logiparin 2500 units daily, $n=8$; Logiparin 3500 units daily, $n=11$). All 27 patients are nevertheless accounted for in the main analysis on an intention to treat basis.

Discontinuation of study treatment before day 8. In addition to the patients who did not receive any injection of study treatment, 68 others prematurely stopped this treatment (one of these patients was not operated on but received the first presurgical injection). The causes for discontinuation are shown in *Table 2*.

Primary efficacy analysis

Incidence of venous thrombosis confirmed by phlebography. Positive FUT scans reported locally led to phlebography in 94 patients (four had two angiograms performed). Out of 64 patients with a central positive FUT reading, three did not have phlebography performed (because the patient or the surgeon refused) and for six patients the films were lost by the local hospital and could not, therefore, be centrally analysed.

The results of FUT scans and angiography as assessed by the Central Angiography Reading Committee are shown in *Tables 3* and *4*; no statistically significant difference between the three groups was observed with respect to the incidence of DVT at day 8. However, if all types of venous thrombosis are accounted for (superficial and/or deep), there was a significantly higher incidence of vein thrombosis in the

Table 2 *Discontinuation of the study treatment*

	Unfract ionated heparin (*n*=429)	Logiparin 2500 units daily (*n*=431)	Logiparin 3500 units daily (*n*=430)	Total (*n*=1290)
No study treatment	6	4	10	20
Operation cancelled	–	–	1	1
Impossibility (no consent, discharge)	5	6	2	13
Haemorrhage	8	4	7	19
Other side effect	–	2	1	3
Deep vein thrombosis suspected	6	14	5	25
Indication of high doses of anti-coagulant	–	4	1	5
Contraindication to anticoagulation	–	1	1	2
Total	25	35	28	88

Table 3 *Positive fibrinogen uptake test*

	Unfract ionated heparin (*n*=429)	Logiparin 2500 units daily (*n*=431)	Logiparin 3500 units daily (*n*=430)	Total (*n*=1290)	*P*
Positive	16 (3·7)	33 (7·7)	15 (3·5)	64 (5·0)	0·007
Positive or doubtful	18 (4·2)	34 (7·9)	16 (3·7)	68 (5·3)	0·01

Global comparison using χ^2 test. Values in parentheses are percentages

Table 4 *Central evaluation of angiography*

	Standard heparin (*n*=429)	Logiparin 2500 units daily (*n*=431)	Logiparin 3500 units daily (*n*=430)	Total (*n*=1290)	*P*
Superficial or DVT before day 8	13 (3·0)	24 (5·6)	10 (2·3)	47	0·03
DVT before day 8	7 (1·6)	16 (3·7)	7 (1·6)	30	0·06
Superficial or DVT during the 1-month follow-up	15 (3·5)	26 (6·0)	11 (2·6)	52	0·03

Global comparison using χ^2 test. Values in parentheses are percentages; DVT, deep vein thrombosis

Logiparin 2500 units daily group. Five additional patients had phlebography performed after discharge for a clinically suspected phlebitis, but the results of these angiograms did not affect the overall results (*Table 4*).

The effect of treatment on venous thrombosis was also evaluated in a multivariate analysis with the main risk factors as covariates (varicose veins, obesity, malignancy, age >60 years). A significant negative effect was still present for Logiparin 2500 units daily ($P=0·01$). No significant difference was observed between UH and Logiparin 3500 units daily ($P=0·52$).

Secondary efficacy analysis

Positive FUT. Sixty-four FUT tests were confirmed as positive by the Central Reading panel. Global comparison using the χ^2 test between the three groups for positive FUT shows a statistically significant difference ($P=0·007$). However, the results of the SH group and the Logiparin 3500 units group are similar (3·7 per cent and 3·5 per cent) (*Table 3*).

Major clinical events. The occurrence of major complications and reinterventions was not statistically different between the three groups. A total of 29 deaths was reported during the trial (respectively 9, 10 and 10 in the UH, Logiparin 2500 units daily and Logiparin 3500 units daily groups). Non-fatal pulmonary embolism was coded certain or possible by the Critical Event Committee for seven patients (UH=2, Logiparin 2500 units daily=4, Logiparin 3500 units daily=1). Surgical reinterventions occurred in 41 patients (UH, $n=13$; Logiparin 2500 units daily, $n=14$; Logiparin 3500 units daily, $n=14$).

Bleeding complications. The effect of each study treatment on the incidence of bleeding complications is summarized in *Table 5*. There were no statistically significant differences between the three groups. On the day of surgical intervention blood loss for incisional loss, or peroperative and early postoperative blood loss were the same in the three groups. During the hospital stay in each group about 10 per cent of patients had haemorrhages; 4 per cent of these haemorrhages required transfusion. From discharge until the visit at 1 month about 3 per cent of patients had haemorrhage, 0·3 per cent needing transfusion.

Severe haemorrhage, defined as haemorrhage needing transfusion and/or reintervention and/or treatment discontinuation, occurred in a total of 36 patients during the study.

Two investigators reported a suspected thrombocytopenia on heparin. The first was only a decrease in platelet count (331×10^9/l on baseline, 204×10^9/l on day 3). Study treatment was Logiparin 3500 units daily which was stopped on day 5 and the thrombocyte count rose to 238×10^9/l. The second was more important (71×10^9/l on day 3, 78×10^9/l on day 5). Study treatment was UH and was stopped on day 8 and the thrombocyte count rose to 98×10^9/l.

Local side effects (mainly local haematoma) were less frequently observed in the Logiparin 2500 units daily group than in the two other groups (*Table 6*).

Table 5 *Haemorrhage and blood loss*

	Unfract ionated heparin (*n*=429)	Logiparin 2500 units daily (*n*=431)	Logiparin 3500 units daily (*n*=430)	Total (*n*=1290)	*P*
Any blood losses					
During operation	33 (7·7)	43 (10·0)	42 (9·8)	118 (9·1)	0·44
Post-operative day 1	14 (3·3)	15 (3·5)	14 (3·3)	43 (3·3)	0·97
Day 2 to discharge	42 (9·8)	43 (10·0)	44 (10·3)	129 (10·0)	0·98
Discharge to 1 month	12 (2·8)	14 (3·2)	10 (2·3)	36 (2·8)	0·7

Global comparison using χ^2 test. Values in parentheses are percentages

Table 6 *Local side effects*

	Standard heparin (*n*=429)	Logiparin 2500 units daily (*n*=431)	Logiparin 3500 units daily (*n*=430)	Total (*n*=1290)	*P*
Haematoma	28	5	21	54	0·000
Pain	9	5	6	20	
Bruising	8	6	6	20	
Other	2	2	2	6	
At least one	37	16	30	83	0·012

Global comparison using χ^2 test

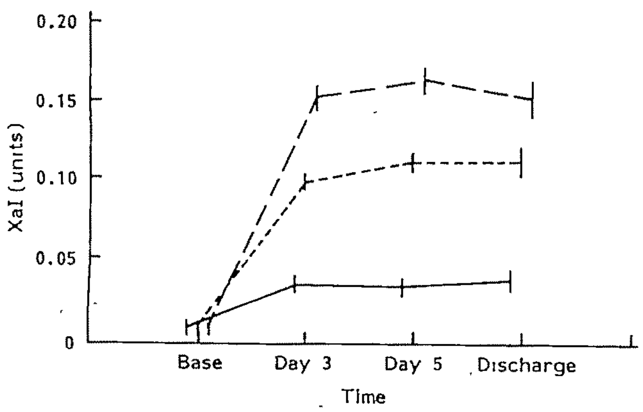

Figure 1 *Evolution of factor Xa inhibitory activity (XaI) with time in the three treatment groups, ——, standard heparin group, —–, Logiparin 2500 units daily group, – – –, Logiparin 3500 units daily group*

Biology

Anti-Xa analysis. All the measurements were performed blindly in a central laboratory using an amidolytic technique with both SH and low molecular weight heparin standards. At baseline, factor XaI activity was similar in the three groups. On day 3, 3 h and 10 h after injection, on day 5 and on discharge, factor XaI activity was significantly higher in the low molecular weight heparin groups than in the UH group, and higher in the Logiparin 3500 units daily group than in the Logiparin 2500 units daily group (*Figure 1*).

Discussion

The present study was designed to evaluate the potential benefit of Logiparin in preventing DVT in patients after surgery compared with low-dose standard heparin, to provide information about the best prophylactic dosage of Logiparin and to evaluate the safety of this medication. The results indicate that there was no difference in the efficacy of Logiparin 3500 units daily and SH 5000 b.d. in preventing postoperative DVT while Logiparin 2500 units daily was significantly less effective than these two regimens. The initial assumption that Logiparin could decrease the incidence of venous thrombosis as compared with SH could not be confirmed.

However, this trial differed in several aspects from other trials assessing the prophylactic effect of heparin in perioperative patients. The diagnosis of DVT was made by FUT and confirmed by phleboangiography. Few trials have adopted this definition for the main end-point. The reliability of both methods has been evaluated by many investigators[9-11]. Although phleboangiography is still considered as the reference method, it may underestimate the occurrence of small transient thrombi, thrombi in formation, and, on the other hand, thrombi older than 3 days The advantages of phleboangiography are the better reliability for femoral thrombi and the distinction between deep and superficial thrombosis, while eliminating false positive FUTs induced by haematoma or superficial thrombophlebitis. It also has the greater advantage of permanent documentation, which can be reviewed whenever necessary.

To compare like with like, it seems fair to compare the incidence of positive FUTs observed in the present trial with those reported in previous trials. In the SH group, the observed rate of positive FUT was 4·2 per cent which could be considered a low incidence. In a review of all trials comparing low-dose SH with controls by Collins *et al.*[1], the overall incidence of positive FUTs in the SH group was 8·9 per cent (in 3966 general surgical patients). However, large variations from one trial to another occurred. It should be stressed that in most of these trials a substantial number of randomized patients were withdrawn from analysis, at least for the FUT end-point, for various reasons, and the effect might be to overestimate the incidence of venous thrombosis. Most trials were performed more than 10 years ago and the present management of surgical patients, surgical techniques, early mobilization and physiotherapy may contribute to the lower incidence of venous thrombosis seen in the present study. In more recent randomized trials, comparing UH and low molecular weight heparins in general surgery, the incidence of positive FUT in the SH groups ranged from 11·9 per cent to 0 per cent[2-8].

Evaluation of the safety of the treatment was one of the secondary aims of the trial. Since haemorrhage is a major concern during anticoagulant therapy, one of the hoped for benefits of low molecular weight heparin was a reduction in bleeding complications. Some studies have reported an increase in bleeding complications with low molecular weight heparin[5,8]. The doses might have been too high in these studies. The choice of the appropriate dose should be made cautiously in view of both the results on DVT and possible side effects. Whether standardization of the units of low molecular weight heparin will help in clarifying the choice of the prophylactic dose is still uncertain since no clear relationship between anti-Xa activity and efficacy as well as side effects has truly been demonstrated. This trial is the first to address the question of the appropriate dose based on clinical end-points. However, practical limitations due to sample size did not allow a study of a wider range of Logiparin doses.

In conclusion, the results of this study demonstrate a significant difference in the efficacy of two doses of Logiparin compared with UH in the prevention of venous thrombosis in surgical patients. Logiparin 2500 units daily was less effective than SH and Logiparin 3500 units daily. The efficacies of Logiparin 3500 units and UH were very similar and led to a low incidence of venous thrombosis. The results are consistent whether one looks at FUT positive tests, any venous thrombosis on phleboangiography or DVT on phleboangiography. The three regimens were well tolerated and there was no difference between the groups in the incidence of major as well as minor undesirable effects. The efficacy and tolerance of Logiparin 3500 units daily compared with UH are consistent with the result observed in previous trials with other low molecular weight heparins.

List of participants

Clinical centres

Dr Sagnard, Prof Dechavanne (biology), Dr White (isotopes), Lyon
Service du Professeur Chabal, Hôpital Edouard Herriot
Dr Combe-Tamzali, Dr Fretault (isotopes) Paris
Service du Professeur Samama, Hôpital Hotel Dieu
Dr Parraguette, Prof Boneu (biology) Toulouse
Service du Professeur Lazorthes, C.H.U. Purpan
Dr Jarrige, Toulouse
Service du Professeur Gouzi, C.H.U. Purpan
Dr Rameil, Nice
Service du Professeur Bourgeon, Hôpital Pasteur
Dr Perrier, Tours
Service du Professeur Brizon, C.H.U Bretonneau
Dr Galland, Angers
Service du Professeur Soret, C.H.U.
Dr Le Querrec, Dr Derlon (biology) Caen
Service du Professeur Gignoux, C.H.U.
Dr Basse-Cathalinat, Dr Caix, Pessac
Service du Professeur Ducassou, Hôpital Pelegrin
Dr Bastenaire, Dr Saint-Paul (biology) Le Chesnay
Centre de Transfusion Sanguine, C H.
Dr Ballestrazzi, Lille
Service du Professeur Mazena, C.H.R
Dr Dupont, Lyon
Service du Professeur Tissot, Hôpital Edouard Herriot
Prof Decousus, Dr Decousus, Saint Etienne
Service du Professeur Queneau, Hôpital de Bellevue
Dr Gille, Lyon
Service du Professeur Partensky, Hôpital Edouard Herriot
Dr Sayag, Dr Azzar (isotopes) Lyon
Service du Professeur Braillon, Hôpital Lyon Sud
Dr Mullet, Lyon
Service du Professeur Dargent, Hôpital Edouard Herriot

Dr Magnet, Lyon
Centre Léon Bérard
Dr Menadier, Lille
Centre Oscar Lambret
Dr Bur, Metz
C H.R. Bon Secours
Dr Geraghty, Glasgow
University Department of Medicine, Royal Infirmary
Prof Carter, Glasgow
Department of Surgery, Royal Infirmary

Coordinating Centre

Clinical Pharmacology Unit, Lyon Mr Alamercery, Prof Boissel, Mr Chevarier, Mrs Gauthier, Mrs Gelas-Dore, Mr Girard, Dr Leizorovicz, Mr Peyrieux, Dr Picolet

Central Reading Centre

Hôpital Cardiologique, Lyon· Prof Amiel, Dr Chirossel, Dr Revel.

Central Biological Laboratory

Laboratoire de Thromboses Expérimentales, Paris Mrs Bara, Mrs Zitoun.

Critical Event Committee

Dr Bouffard, Hôpital Edouard Herriot, Lyon
Dr Moleur, Clinique Chartreuse, Voiron
Dr Vital Durand, Centre Hospitalier Lyon-Sud, Lyon

Steering Committee

Dr Andersen, Novo Laboratories, Denmark
Prof Boissel, Clinical Pharmacology Unit, Lyon
Dr Geraghty, Royal Infirmary, Glasgow
Dr Leizorovicz, Clinical Pharmacology Unit, Lyon
Dr Marchal, Hôpital Bretonneau, Tours
Prof Samama (Chairman) , Hôpital Hotel Dieu, Paris
Dr Squiban, Novo Laboratories, Paris

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Comparison of different vascular prostheses and matrices in relation to endothelial seeding

R. Vohra,
G. J. L. Thomson,
H. M. H. Carr,
H. Sharma and
M. G. Walker

Department of Vascular Surgery and Medical Biophysics, Manchester Royal Infirmary and Manchester Medical School, Manchester, UK

Correspondence to:
Mr M. G. Walker, Department of Vascular Surgery, Manchester Royal Infirmary, Oxford Rd., Manchester M13 9WL, UK

Thin-walled expanded polytetrafluoroethylene (ePTFE), woven Dacron® and gelatin-impregnated Dacron (Gelseal®) vascular grafts were compared, the grafts being coated with three different matrices: collagen IV, fibronectin and preclot matrix. In addition, untreated ePTFE and Gelseal were examined. The graft segments, coated with these matrices, were incubated with radiolabelled adult human endothelial cells for 30, 60 and 90 min. Endothelial cell adherence was calculated from the ratio of radioactive counts in the grafts to counts in grafts plus supernatants. Endothelial cell attachment to untreated grafts was poor, but a suitable matrix significantly improved adherence. All three matrices tested gave good results, although preclot was best; 30–60 min incubation was sufficient for optimum cell attachment. Cell adherence to both Dacron and ePTFE was significantly better than to Gelseal. The type of prosthetic polymer and the substrate protein coating used to promote endothelial cell adherence are two important factors which may determine the ultimate success of endothelial seeding in the operating room.

Synthetic vascular prostheses are inherently thrombogenic, especially in low flow situations and, since endothelium is the most non-thrombogenic surface known, attempts have been made to provide such prostheses with an active endothelial lining[1–3]. Endothelial cell seeded canine grafts have resulted in improved patency and reduced platelet adhesion[4,5].

Both Dacron® (E.I. du Pont de Nemours and Company, UK) and expanded polytetrafluoroethylene (ePTFE, W.L. Gore and Associates) have been successfully seeded with endothelial cells, achieving confluent monolayers *in vitro* as well as *in vivo* in animal experiments[1–3,6–9], but these grafts, coated with different matrices, have not been directly compared with each other when seeded. The aim of this study was to compare the endothelial seeding efficiency of these two grafts. The role of different basement membrane proteins as substrate matrices for attachment of cells was also compared.

Materials and methods

Endothelial cell cultures

Adult human endothelial cells were enzymatically harvested from saphenous vein segments. The cells were grown in 25 cm² flasks and cell lines were established by dividing the cells in a ratio of 1:3. Endothelial cell identity was established by their positivity for factor VIII related antigen and positive lectin staining.

Vascular prostheses and experimental design

Three types of grafts were compared: thin-walled ePTFE, Cooley VERI-SOFT® woven Dacron (Meadox Medicals, Incorporated) and Gelseal® (Vascutek Ltd., Inchinnan, UK).

Preclot, collagen IV and fibronectin matrices were used for each graft. Adherence assays were also performed with ePTFE coated with medium to determine the latter's effect in promoting cell adhesion as the fibronectin solution was diluted with medium. In addition there was an untreated group for ePTFE and for Gelseal. Cell adherence to untreated Dacron was not feasible because of the inevitable leakage of fluid through the untreated graft. Incubation for 30, 60 and 90 min was used in each group. Ten graft segments were studied in each subgroup. Each graft segment was 4 cm long with a 6 mm diameter.

Coating of grafts with matrices

Preclot matrix was obtained by filling the graft segment with blood and leaving it for 90 min. At the end of this period, the graft was washed gently with phosphate buffered saline. Fibronectin coating was achieved by incubating in 50 μg/ml fibronectin solution (Blood Products Laboratory, Elstree, UK) at 37°C for 90 min[10]. Collagen IV (Sigma Chemical Company, St. Louis, Missouri, USA) was dissolved in 0·01 M acetic acid for 24 h and neutralized with 0·5 ml of 1 M sodium hydroxide solution. A coating of collagen IV on the graft was achieved by incubating the graft with 0·5 mg/ml collagen solution at room temperature for 90 min.

Labelling of endothelial cells

Endothelial cells were labelled by a modification of the method described by Sharefkin *et al.*[11], labelling efficiency being calculated allowing 30 min for initial leakage of indium. At this stage, the cells were washed again before use.

Endothelial cell seeding of grafts

Equal aliquots of $3–4 \times 10^5$ radiolabelled endothelial cells per graft segment were resuspended in 0·5 ml of medium and the graft was incubated in the suspension for the required time. After incubation, the supernatant and graft were collected for γ-counting. Endothelial cell adherence was calculated as follows:

$$\text{Seeding efficiency} = \frac{\text{Counts in graft}}{\text{Counts in graft and supernatant}} \times 100$$

Qualitative analysis of seeded grafts

Graft segments from each subgroup were stained with haematoxylin for light microscopy, and fixation in 2·5 per cent glutaraldehyde in 0·1 M sodium cacodylate buffer at pH 7·4 was used for scanning electron microscopy. Cell attachment and spreading on grafts coated with protein matrices or otherwise was studied.

Statistics

Analysis of variance and Duncan's ranges were calculated using SPSS-X RELEASE version 3.1 software (SPSS Statistical Software, Los Angeles, California, USA).

Results

Endothelial cell adherence at 60 min and comparison of matrices

Cell adherence to preclot, fibronectin and collagen matrices on ePTFE was better than to untreated grafts and to grafts treated with medium alone ($P < 0·05$). Although preclot and fibronectin were both significantly better than collagen, preclot matrix was

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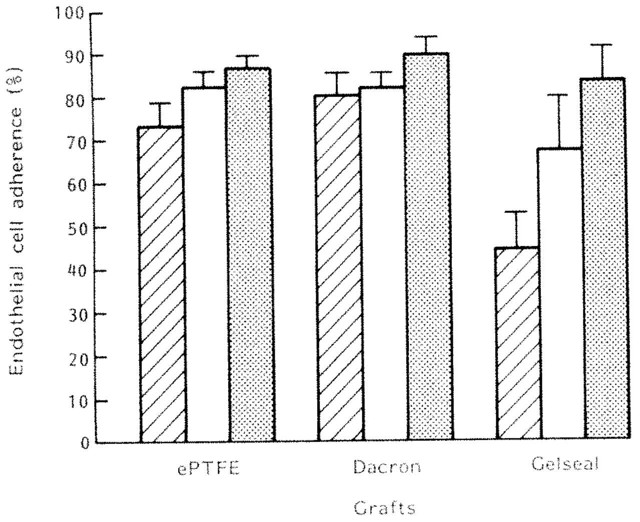

Figure 1 *Endothelial cell adherence to three different grafts coated with three different matrices at 60 min.* ▨, *Collagen;* ☐, *fibronectin;* ▩, *preclot*

best. Although there was no quantitative measure of cell attachment on untreated Dacron, it was evident from scanning electron microscopy that this was poor. Cell adherence on Dacron coated with preclot matrix was significantly better compared with Dacron coated with fibronectin and collagen ($P<0.05$). Endothelial cell adherence to Gelseal grafts coated with preclot and fibronectin was significantly better than adherence to collagen treated or untreated grafts ($P<0.05$) and preclot matrix was better than fibronectin. Collagen IV did not improve cell adherence to Gelseal (*Figure 1* and *Tables 1, 2* and *3*).

Endothelial cell adherence at 60 min and comparison of grafts

Endothelial cell adherence to the three grafts coated with collagen was significantly better in Dacron than in ePTFE and Gelseal ($P<0.05$). Adherence was significantly less in Gelseal than in ePTFE ($P<0.05$). When grafts were coated with fibronectin, significantly higher endothelial cell attachment was noted with Dacron and ePTFE compared with Gelseal ($P<0.05$). Using preclot, cell attachments to ePTFE and Dacron were similar; the only significant difference was that Gelseal had poorer cell adherence than Dacron ($P<0.05$) (*Figure 1*). There was significantly higher endothelial cell adherence to untreated Gelseal compared with untreated ePTFE ($P<0.001$) (*Figure 2*).

Endothelial cell adherence and comparison of incubation times

Endothelial cell adherence at 30, 60 and 90 min was similar in all subgroups except for preclot matrix on ePTFE and collagen matrix on Gelseal ($P<0.04$ and $P<0.01$ respectively). However, optimal cell attachment occurred between 30 and 60 min, no advantage being gained by incubating for 90 min (*Tables 1–3*).

Qualitative results

Light microscopy revealed significant cell adherence to ePTFE and Dacron coated with the three matrices. Scanning electron microscopy of uncoated ePTFE and Dacron showed a few rounded, smooth-surfaced cells which had not spread (*Figure 3*), whereas with coated grafts the cells were rough and spread was evident (*Figures 4* and *5*). Endothelial cells attached to Dacron appeared thinner and more stretched out than those on ePTFE. The cells were also seen adhering in the crevices of Dacron as well as attaching to the sides of individual fibres (*Figure 4*). There was a tendency to attach to the nodes of ePTFE rather than internodular fibrils (*Figure 5*). On ePTFE

Table 1 *Endothelial cell adherence to ePTFE graft coated with different matrices*

	Incubation time		
Matrix	30 min	60 min	90 min
None	2·7(1·0)	3·9(2·8)	4·2(2·8)
Medium	13·1(6·4)	17·6(9·9)	15·4(6·8)
Collagen	75·6(8·8)	73·2(5·6)	78·8(3·0)
Fibronectin	78·1(6·5)	82·5(3·5)	79·0(3·5)
Preclot	84·4(4·8)	86·6(3·2)	88·6(1·9)

Values given are percentage(s.d.)

Table 2 *Endothelial cell adherence to Dacron graft coated with different matrices*

	Incubation time		
Matrix	30 min	60 min	90 min
Collagen	77·3(3·8)	80·2(5·1)	80·7(4·7)
Fibronectin	84·1(3·4)	82·0(3·5)	83·5(4·6)
Preclot	88·9(3·4)	89·8(3·9)	90·4(3·1)

Values given are percentage(s.d.)

Table 3 *Endothelial cell adherence to Gelseal graft coated with different matrices*

	Incubation time		
Matrix	30 min	60 min	90 min
None	46·6(9·3)	43·7(10·1)	49·4(9·9)
Collagen	36·0(9·6)	46·5(5·7)	49·0(9·5)
Fibronectin	59·6(8·3)	67·3(12·5)	66·5(7·7)
Preclot	82·4(3·8)	83·4(7·8)	78·2(4·4)

Values given are percentage(s.d.)

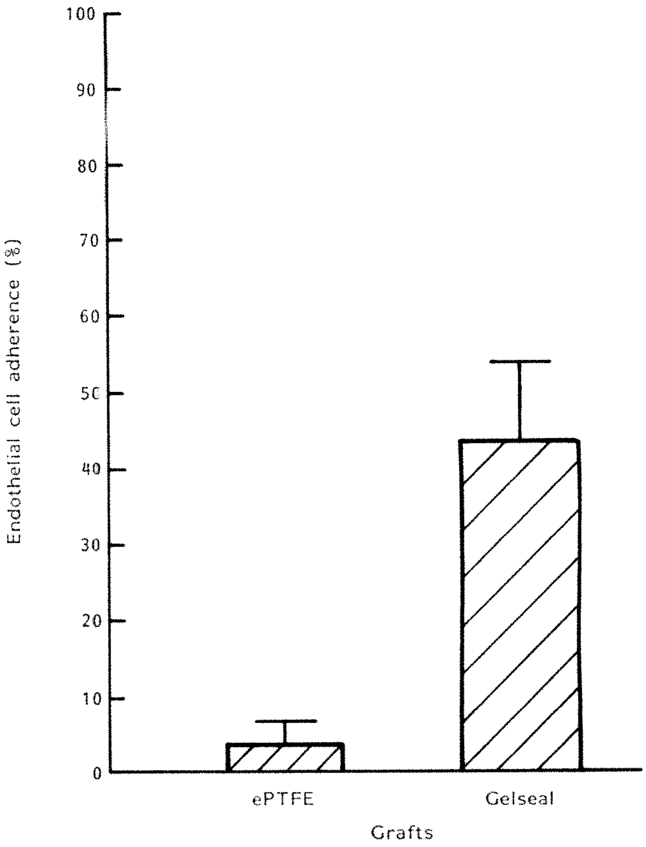

Figure 2 *Endothelial cell adherence to uncoated ePTFE and Gelseal at 60 min*

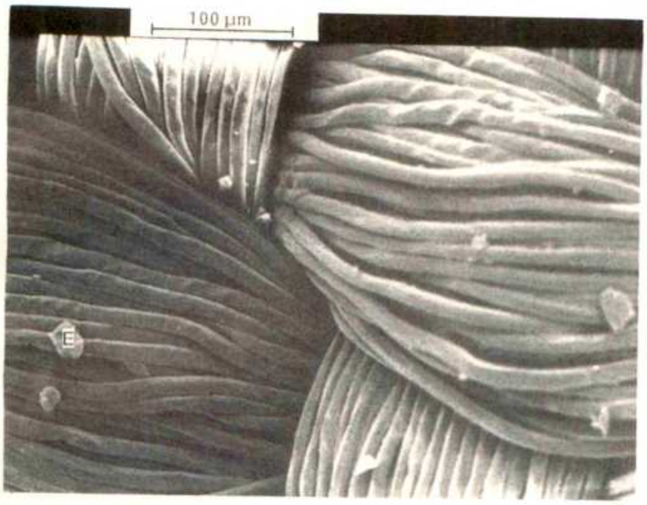

Figure 3 *Scanning electron micrograph of uncoated Dacron graft showing a few rounded and smooth endothelial cells (E)*

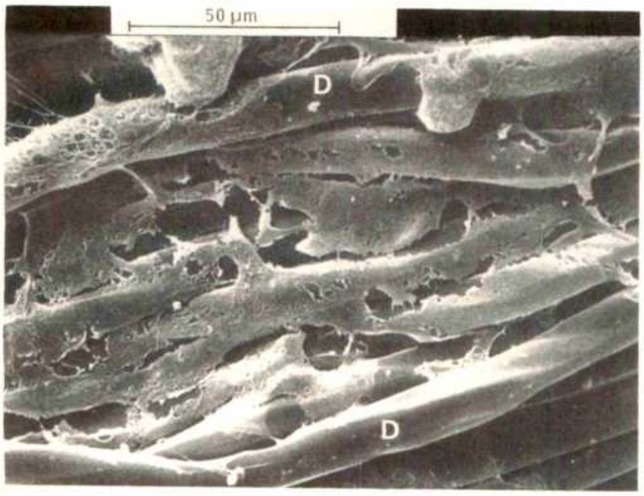

Figure 4 *Scanning electron micrograph of preclot-coated Dacron showing endothelial cells adhering in the crevices as well as attaching to the sides of individual Dacron fibres (D)*

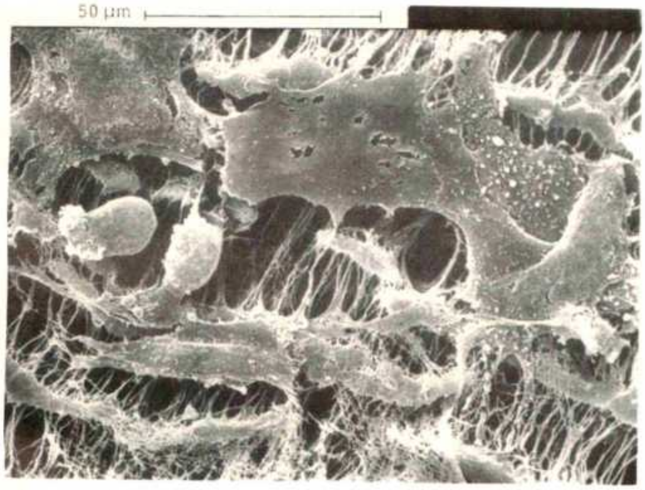

Figure 5 *Scanning electron micrograph of preclot-coated ePTFE showing rough and spread out endothelial cells with a tendency to attach to nodes*

the cells appeared more regular and less thinned out, anchoring themselves to the internodular areas with pseudopodia-like processes around the fibrils (*Figure 6*). Cell attachment to and spreading on Gelseal was very similar to that of Dacron, the only significant difference being that cell attachment and spreading occurred even on uncoated Gelseal.

Discussion

Adherence assays in this study were performed using indium-111 oxine labelled endothelial cells. A modification of the technique described by Sharefkin *et al.*[11] was used to label endothelial cells giving a high labelling efficiency with a predictable spontaneous leakage of isotope. Image analysis with a grid counter was tried but radiolabelling of endothelial cells was found to be more reliable for quantitative analysis.

A variety of protein substrates have been used by other investigators to improve endothelial cell adherence to vascular prostheses[7,9,12–14]. There is a consensus of opinion that laminin is not a suitable substrate for initial endothelial cell attachment at the time of seeding. Hasson *et al.*[9] found 28 per cent attachment to laminin-coated polystyrene compared with 63 and 60 per cent attachment to polystyrene coated with fibronectin and gelatine respectively. Previous studies from our laboratory have shown similar results[15]. Anderson *et al.*[7] in their adherence studies of ePTFE showed no improvement with laminin compared with untreated grafts. These workers also showed that laminin combined with either fibronectin or preclot was less effective as a matrix than fibronectin or preclot used alone.

Anderson *et al.*[7] used collagen I on ePTFE in their experiments and found significantly better endothelial cell adherence when compared with fibrin or fibronectin. Pratt *et al.*[13] used a mixture of collagen I and III on polystyrene in their study, achieving a significant improvement in cell adherence. Collagen IV was compared in the present study with fibronectin and preclot matrices. Endothelial cell attachment to collagen-coated ePTFE, Dacron and Gelseal grafts at 60 min was 73, 80 and 47 per cent respectively, which was significantly less than the cell adherence achieved with the other two matrices.

Fibronectin has been investigated extensively regarding its ability to enhance the attachment of endothelial cells to ePTFE[14,16]. Kesler *et al.*[16] found 90 per cent cell attachment to ePTFE grafts coated with fibronectin compared with 63 per cent attachment to those coated with preclot matrix. In another study a significant improvement in endothelial cell adherence to fibronectin-coated grafts was noted[17]. On the other hand, Lindblad *et al.*[12] found that cell attachment to fibronectin-coated surfaces was less than that to surfaces coated with blood. In the present study cell adherence to fibronectin-coated ePTFE was 83 per cent after 60 min incubation. Results with fibronectin-coated Dacron were similar (*Tables 1* and *2*).

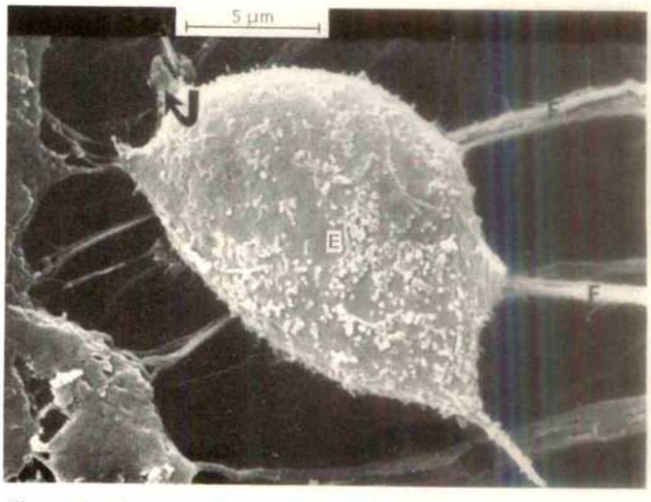

Figure 6 *Scanning electron micrograph of collagen-coated ePTFE showing adaptation of endothelial cell (E) about to anchor around the ePTFE fibrils (F) (arrowed)*

As fibronectin was diluted in culture medium, it is possible that wetting the graft with medium improved endothelial cell adherence compared with uncoated grafts. Therefore endothelial cell adherence studies with ePTFE coated with medium were performed. Although this improved cell adherence significantly ($P<0{\cdot}05$) compared with untreated grafts, adherence was significantly less than in grafts coated with fibronectin ($P<0{\cdot}05$). Thus improved adherence of endothelial cells on grafts coated with fibronectin solution was caused by fibronectin itself.

A higher cell adherence with Gelseal had been expected because of fibronectin's known binding sites for gelatine, but surprisingly adherence to Gelseal coated with fibronectin in this study was lower than that to woven Dacron coated with fibronectin.

In this study, endothelial cells were seeded on a preformed preclot matrix, in contrast to the method followed in the initial studies[2,18] in which endothelial cells were mixed with the blood used to preclot the grafts. These two techniques were compared by Lindblad *et al.*[12], who found the former to be superior. Maximal cell attachment for ePTFE, Dacron and Gelseal coated with preclot was 87, 90 and 83 per cent respectively at 60 min. These results were significantly better than those achieved with fibronectin and collagen IV matrices in the present study. Superior endothelial cell adherence with preclot matrix compared with fibronectin was also noted by other workers[12].

It is clear from this study that most endothelial cells adhere to the graft by 30 min as there was no statistically significant difference between cell adherence at different periods of incubation. This was true for all subgroups of different matrices and grafts, except preclot matrix on ePTFE and collagen matrix on Gelseal. Significantly higher cell adherence was achieved at 90 min in the latter two. Other workers have observed that cell attachment to ePTFE was essentially complete with 15 min incubation for cells suspended in phosphate buffered saline[7].

Cell attachment to Dacron and ePTFE was significantly higher than to Gelseal with all the three matrices tested. Although cell adherence to Dacron was higher than to ePTFE with all three matrices, it was statistically significant only with collagen. In a comparative study of endothelial cell adherence to Dacron and ePTFE grafts, Sharefkin *et al.* found 70 per cent attachment to Dacron compared with only 12 per cent to ePTFE (personal communication). However, the coverage of implanted grafts at 4 weeks was similar in both Dacron and ePTFE. In another study, comparing two grafts after endothelial seeding, a more rapid rate of *in vivo* endothelialization occurred in ePTFE grafts than in Dacron[3].

Foxall *et al.*[1] noted in their *in vitro* experiments that Dacron was less suitable for endothelial cell growth even after coating with collagen and fibronectin, because of its uneven and irregular surface. Apart from this, Dacron also has ridges and indentations due to crimping. Scanning electron micrographs in the present study confirmed the findings of these authors. Endothelial cells attached to Dacron appeared thinned and stretched out, whereas cells on ePTFE appeared more regular. On Dacron, the cells were seen in crevices, on sides and under surfaces of fibres (*Figure 4*). There was selective endothelial cell attachment to the nodes of ePTFE. These cells displayed an unusual adaptation to the atypical environment by anchoring themselves to the internodular fibrils (*Figures 5* and *6*).

In conclusion, endothelial cell attachment to an untreated graft was poor. A suitable matrix significantly improved adherence. All matrices tested gave good results, although preclot was best. Incubation of endothelial cells for 30 min was sufficient for optimum cell attachment. Quantitatively, cell adherence to both Dacron and ePTFE grafts was significantly better than adherence to Gelseal. Distinct cellular morphological features were noted on scanning electron microscopy for all grafts, which may well have important long-term implications for endothelialization.

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Spontaneous abdominal arteriovenous fistulae: report of eight cases and review of the literature

G. L. Gilling-Smith and A. O. Mansfield

Department of Vascular Surgery, St. Mary's Hospital, London, UK
Correspondence to:
Mr G. L. Gilling-Smith,
Department of Surgery, Royal Postgraduate Medical School,
Hammersmith Hospital, London
W12 0NN, UK

The spontaneous rupture of an abdominal aneurysm into an adjacent major vein results in a profound and rapidly worsening haemodynamic disturbance. Survival depends on prompt diagnosis and closure of the fistula at operation. Eight cases are reported and modes of presentation, diagnostic criteria and management principles are reviewed in a detailed analysis of 148 cases in the English literature.

The spontaneous rupture of an abdominal aortic aneurysm into the vena cava was first reported by James Syme in 1831[1]. Reviewing the literature in 1955, Boffi[2] found only 26 cases, none of whom had survived. Surgical repair of a spontaneous aortocaval fistula was first attempted by Lehman in 1935[3], but the patient died 15 h after quadruple ligation of the aorta and inferior vena cava. Cooley[4] claimed the first successful repair 20 years later.

Since then, a further 140 cases of spontaneous abdominal arteriovenous fistula have been reported[5–83]. Such fistulae are found in less than 4 per cent of ruptured abdominal aneurysms[8,13]. As the prevalence of aneurysmal disease increases, they are likely to be encountered more frequently. Prompt recognition of this condition is important if such cases are to be treated successfully.

We report a further eight cases which illustrate the variety of clinical presentation and difficulties in diagnosis of this condition. They include the first reported case of a pelvic renal artery aneurysm which had ruptured into the renal vein and a case of iliac artery aneurysm which had ruptured into both iliac veins.

Case reports

Between 1980 and 1989, 123 patients underwent operation for ruptured abdominal aortic or iliac aneurysm at St. Mary's Hospital in London. Seven (6 per cent) of these had ruptured into the inferior vena cava or common iliac vein. During the same period one patient underwent operation for a fistula between a renal artery aneurysm in a pelvic kidney and the adjacent renal vein. The clinical features and operative findings are summarized in *Table 1*.

Symptoms and signs

Five patients (cases 1–5) presented acutely with abdominal or low back pain and a palpable abdominal aneurysm. Three of these (cases 2, 3 and 4) were clinically shocked and retroperitoneal rupture was diagnosed. In the other two, a machinery bruit and widened pulse pressure, together with a high central venous pressure (case 1) or evidence of regional venous hypertension (case 5), prompted a preoperative diagnosis of aortocaval fistula. One patient (case 6) presented with a 10-week history of intermittent left iliac fossa pain, lethargy and weakness. A palpable aortoiliac aneurysm and systolic abdominal bruit suggested an aortocaval fistula. Serum creatinine was moderately raised (283 μmol/l) and digital subtraction angiography, performed to delineate the renal arteries, revealed a fistula between a left common iliac aneurysm and left iliac vein.

Two patients (cases 7 and 8) had been treated unsuccessfully for worsening cardiac failure for over 2 years and were referred for surgical opinion when a pulsating abdominal mass and machinery abdominal bruit were noted. The diagnosis of aortocaval fistula was further supported by the finding of a wide pulse pressure and cyanosis of the lower limbs.

A major arteriovenous fistula was thus suspected or proven before operation in five patients (cases 1, 5, 6, 7 and 8). In the remaining three patients (cases 2, 3 and 4), retroperitoneal rupture of an abdominal aortic aneurysm was confirmed at laparotomy. In addition, however, a powerful machinery thrill (cases 2 and 3), unexpected high central venous pressure (cases 2 and 4) and pulsatile venous bleeding (case 4) suggested coexistent rupture into a major vein. In all eight cases, therefore, profuse venous haemorrhage was anticipated before incision of the aneurysm and evacuation of thrombus.

Operative management

In six patients (cases 1–5 and 7), the aneurysm was incised and thrombus evacuated after obtaining both proximal and distal arterial control in the usual way. In one patient (case 6) a left common iliac aneurysm was continuous with an aneurysm of the left internal iliac artery and distal control could not be obtained without hazardous pelvic dissection. On opening the aneurysm, bleeding from branches of the internal iliac artery was controlled digitally while the ostia were sutured. Haemorrhage from the fistula was controlled in six patients by either digital compression (cases 1 and 2), balloon occlusion catheters (cases 3, 4 and 6) or clamps (case 5). Mean blood loss was 4300 ml (range 2200–7000 ml). In one patient (case 7 – fistulae into both common iliac veins) adequate control could not be obtained despite balloon catheter occlusion of the iliac veins, cross-clamping of the inferior vena cava and compression of the pelvic veins with packs. Measured blood loss was 23 000 ml. In six patients the fistula was closed by suture from within the aneurysm sac. In one (case 4) the vena cava was dissected free and repaired directly. Routine inlay aortoiliac grafting was then performed in these seven cases. One patient (case 8) underwent nephrectomy after cross-clamping of renal artery and vein. Blood loss was minimal.

Outcome

In six patients (cases 1–6) closure of the fistula resulted in an immediate improvement in general condition. The central venous pressure returned to normal and in five cases there was a prompt diuresis. One patient (case 6) required haemodialysis on the second and fourth days after operation because of persistent oliguria. Thereafter renal function started to improve and was normal by time of discharge. Recovery after operation was otherwise uneventful in these six patients and all were free of complications at last follow-up (range 3 months–4 years).

In contrast, the two patients who had presented in gross chronic congestive cardiac failure did not improve. In one (case 7) the additional insult of massive fluid losses at operation resulted in progressive multisystem failure and intractable coagulopathy. He died on the tenth day after operation. The second patient (case 8) remained in congestive cardiac failure, developed bronchopneumonia and died 25 days after surgery.

Review of the literature

We have reviewed 148 cases of spontaneous abdominal arteriovenous fistula reported since 1955. In 142 of these, the fistula resulted from the rupture of an atherosclerotic aneurysm. Three cases were associated with syphilitic aortitis[3,11,73], two

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Table 1 *Symptoms, signs and operative findings in eight cases of spontaneous abdominal arteriovenous fistula*

Case	Sex	Age (years)	Symptoms/duration	Signs	Operative findings	Procedure	Outcome
1	F	72	Low back pain, 2 weeks; dyspnoea, 4 days	Palpable AAA – machinery bruit; BP 120/50 mmHg; CVP + 30 cmH$_2$O	Infrarenal AAA (12 cm); fistula into IVC (2 cm)	Fistula sutured; bifurcation graft	Well, 2 years
2	M	67	Low back pain, 2 days	Palpable AAA; BP 70/– mmHg	Infrarenal AAA (11 cm); retroperitoneal rupture; fistula into IVC (3 cm); (CVP + 32 cmH$_2$O)	Fistula sutured; bifurcation graft	Well, 4 years
3	M	80	Low back pain, 4 days	Palpable AAA; BP 80/– mmHg	Infrarenal AAA (12 cm); retroperitoneal rupture; fistula into IVC (4 cm) (machinery thrill)	Fistula sutured; straight graft	Well, 1 year
4	M	81	Back pain, 10 days; abdominal pain, 2 days	Palpable AAA – tender; BP 100/60 mmHg	Infrarenal AAA (10 cm); retroperitoneal rupture; fistula into IVC (2 cm); (CVP + 24 cmH$_2$O)	Fistula sutured; bifurcation graft	Well, 1 year
5	M	65	Back pain, 2 weeks; haematuria, 2 days	Palpable AAA – machinery bruit; BP 110/20 mmHg; cyanotic legs; priapism and pulsating varicose veins	Aorto right iliac aneurysm; fistula: right CIA into IVC (3 cm)	Fistula sutured; bifurcation graft	Well, 6 months
6	F	73	LIF pain, weakness and lethargy, 10 weeks; vomiting, 1 week	Palpable aortoiliac aneurysm; systolic bruit; BP 150/70 mmHg; acute renal failure	Aorto left iliac aneurysm; fistula: left CIA into left CIV (machinery thrill, CVP + 20 cmH$_2$O)	Fistula sutured; bifurcation graft	Well, 3 months
7	M	66	Dyspnoea, 3 years; swollen legs, 2 years	Pulsating RIF mass – machinery bruit; BP 140/40 mmHg; CVP + 28 cmH$_2$O; gross pulmonary oedema; cyanotic legs	Right CIA aneurysm; fistulae into both CIVs	Fistulae sutured; iliac graft	Died, 10 days
8	F	73	Dyspnoea, 4 years; swollen legs, 3 years	Pulsating RIF mass – machinery bruit; BP 130/60 mmHg; CVP + 22 cmH$_2$O	Pelvic right kidney; right renal artery aneurysm; fistula into right renal vein	Right nephrectomy	Died, 25 days

AAA, abdominal aortic aneurysm; IVC, inferior vena cava; CIA, common iliac artery; CIV, common iliac vein; LIF/RIF, left/right iliac fossa; BP, blood pressure; CVP, central venous pressure

Table 2 *Site of spontaneous abdominal arteriovenous fistula in 148 cases reported since 1955*

Aneurysm	Vein	*n*	References
Aorta	IVC (right-sided)	113	
	IVC (left-sided)	2	21, 47
	Left renal vein (retroaortic)	7	30, 34, 37, 49, 56, 59, 82
	Left renal vein (preaortic)	1	74
	Lumbar vein	1	27
	Right CIV	2	1, 48
	Left CIV	2	18, 20
Right CIA	Right CIV	5	9, 41, 54, 65, 83
	Left CIV	2	9, 43
	Both CIVs	1	Case 7
	IVC	4	Case 5, refs. 9, 57, 80
Left CIA	Left CIV	7	Case 6, refs. 11, 20, 25,27, 39, 64
Renal renal artery	Right renal vein	1	Case 8

IVC, inferior vena cava; CIA, common iliac artery; CIV, common iliac vein

with inflammatory aneurysm[39] and one with cystic medionecrosis of Marfan's syndrome[33]. Only nine cases (6 per cent) were reported in women, a smaller sex ratio than for atherosclerotic aneurysms in general. Average age was 67 years (range 41–91 years) excluding the cases of syphilis (34, 37 and 42 years) and Marfan's syndrome (21 years). In 113 cases (76 per cent) an infrarenal abdominal aortic aneurysm ruptured into a normally situated inferior vena cava. The site of rupture in the remaining 35 cases is given in *Table 2*.

The haemodynamic effects of a major arteriovenous fistula have been studied both experimentally and clinically[84–88]. Blood is diverted through the fistula from the high resistance arterial circuit into the low resistance high capacitance venous circuit. Central venous pressure and venous return increase, while a fall in mean systemic arterial pressure results in reduced effective systemic blood flow. There is a compensatory increase in both cardiac output and plasma volume. The chambers of the heart enlarge until decompensation results in high output cardiac failure. The magnitude of these changes depends on the size of the fistula, the duration of the haemodynamic disturbance and the cardiovascular reserve of the patient; hence the effects of a spontaneous abdominal arteriovenous fistula are often dramatic. There is a tendency for the fistula to enlarge progressively[22] and elderly patients may have coexistent coronary artery disease and poor cardiovascular reserve.

Livingstone *et al.*[48] demonstrated in canine experiments that the caudal direction of flow through an aortocaval fistula results in a venous pressure gradient across the fistula. Venous hypertension distal to the fistula, which may be further increased if the proximal great veins are compressed by the aneurysm, results in cyanosis and oedema of the lower limbs (unilateral in the case of an iliac fistula[54]) and engorgement of the superficial veins in both bladder[77] and rectal mucosae[79].

The 'distinct syndrome'[9,61,72] of aortocaval fistula is thus easily recognized. A painful aneurysm is palpable and a loud machinery murmur with systolic accentuation is audible over the entire abdomen. High output cardiac failure is characterized by a bounding 'water hammer' pulse, widened pulse pressure, elevated central venous pressure and pulmonary oedema. Reduced systemic perfusion results in varying degrees of confusion[9,27], lethargy[43,60] and renal failure[13,75]. Manifestations of regional venous hypertension include lower limb cyanosis and oedema[9,22], pulsating varicose veins[16], haematuria[12], rectal bleeding[79] and priapism[35,52].

Analysis of the signs and symptoms in 148 reported cases (*Table 3*) reveals that such a classic presentation is uncommon. Three distinct modes of presentation are recognized. Ninety-four patients (63 per cent) presented with abdominal or back pain and a palpable (but rarely tender) abdominal aneurysm. None was clinically shocked. Duration of symptoms ranged from 3 h to 4 months (mean 19 days). The triad of machinery murmur, high output cardiac failure and regional venous hypertension was found in only 25 of these patients. All but four, however, had at least one of these features. A fistula was diagnosed clinically in 54 patients and following angiography in a further 16. The remaining 24 patients underwent laparotomy with a diagnosis of threatened rupture.

A further 36 patients (24 per cent) presented acutely (symptoms <48 h) with a tender abdominal aneurysm and profound cardiovascular collapse. All underwent urgent laparotomy with a clinical diagnosis of retroperitoneal rupture. In 22 of these an abdominal bruit (18) or regional venous hypertension (10) was noted before operation and coexistent rupture into a major vein was suspected. In 16 patients no retroperitoneal rupture was found at operation (prompting consideration of an alternative diagnosis) while in eight patients a thrill (4), pulsatile venous bleeding (3) or paradoxical elevation of the central venous pressure (2) warned the surgeon of a fistula before incision of the aneurysm sac. Thus in this group of patients only six (17 per cent) had neither preoperative nor intraoperative features to suggest an arteriovenous fistula.

A third group of 15 patients (10 per cent), in whom an abdominal aneurysm was not palpable, presented in chronic congestive cardiac failure refractory to medical treatment. Duration of symptoms ranged from 1 week to 8 months (mean 6·3 weeks). In nine of these a systolic (6) or machinery (3) abdominal bruit was heard and a fistula was diagnosed at angiography (7) or clinically (2) following identification of an aortic aneurysm on abdominal radiography. In two patients a significant arteriovenous shunt was detected at cardiac catheterization and the site of the fistula confirmed angiographically. Three patients died without operation and the fistula was identified at autopsy. One patient developed a swollen leg and was prepared for iliac vein thrombectomy but pulsatile venous bleeding at operation alerted the surgeon to an iliac arteriovenous fistula.

Table 3 *Frequency of signs and symptoms in 148 cases of spontaneous abdominal arteriovenous fistula*

	n
Signs	
Palpable abdominal aneurysm	130 (88)
Bruit	110 (74)
Evidence of high output cardiac failure	59 (40)
Elevated JVP/CVP	48
Pulmonary oedema	35
Wide pulse pressure	49 (33)
Evidence of regional venous hypertension	77 (52)
Regional oedema (lower limbs)	53
Regional cyanosis (lower limbs)	34
Haematuria	26
Pulsating varicose veins	9
Rectal bleeding	3
Priapism	4
Symptoms	
Abdominal pain	74 (50)
Low back pain	63 (42)
Radiation to hips/thighs	33 (22)
Dyspnoea	62 (42)
'Swollen legs'	4

Values in parentheses are percentages; JVP/CVP, jugular/central venous pressure

In three cases the presentation was obscure. Two patients presented with abdominal pain and frank haematuria. An abdominal aortic aneurysm was noted during intravenous pyelography and a fistula was demonstrated at angiography. One patient presented in renal failure. A fistula was an unexpected finding at angiography.

Seven patients were managed conservatively, either because the diagnosis was not suspected[18,23,43,47] or because the patient was considered too ill for operation[63,76,79]. All died from intractable congestive cardiac failure. A further two patients died before operation could be performed[7,40]. The remaining 139 patients underwent laparotomy. Operation was delayed in 19 of these while attempts were made to improve their condition medically. In all cases congestive cardiac failure was refractory to digitalis and diuretic therapy and was aggravated by transfusion.

At operation haemorrhage from the fistula was controlled by digital compression of the vena cava in 70 cases, cross-clamping of the vena cava in 21 cases and balloon occlusion catheters in 12 cases. Method of control was not reported in 36 cases. The fistula was most commonly closed by suture of the vein wall from within the aneurysm sac. In nine cases the inferior vena cava was ligated above and below the fistula. No long-term complications were reported[12,16,21,32,41–43,55,62]. In three cases[30,59,74] the left renal vein was ligated and in one case[52] a small Dacron® (E.I. du Pont de Nemours and Co., UK) patch was used to close the fistula. In all cases the operation was completed by routine aortoiliac grafting.

Nine patients died at operation. In six of these death was due to profound hypovolaemia secondary to haemorrhage from the fistula. In one, death was attributed to the sudden and severe alteration in haemodynamics following aortic cross-clamping[5]. One patient died from cardiac failure precipitated by preoperative transfusion[8] and one from pulmonary embolism following manipulation of the aneurysm[38]. There were 27 deaths after operation during the same hospital admission. Primary causes of death were reported as myocardial infarction in six cases, renal failure in five and bronchopneumonia complicating persistent congestive cardiac failure in four cases. Four deaths were attributed to pulmonary embolism, one secondary to thrombosis at the site of fistula repair[8]. Two patients died from digitalis intoxication[43], one inhaled vomit[73] and one died following accidental air embolism through a central venous catheter[59]. The remaining four patients died from septicaemia, intractable coagulopathy and 'multisystem failure'.

There were 103 long-term survivors, resulting in an overall reported mortality rate for this condition of 30 per cent, and a mortality rate of 26 per cent for those undergoing operation. The mortality rate was higher in patients with coexistent retroperitoneal rupture (48 per cent compared with 21 per cent for fistula alone). Diagnosis of a fistula before incision of the aneurysm sac was associated with a lower mortality rate (24 per cent) than 'discovery' after evacuation of aneurysm thrombus (33 per cent). A decrease in mortality rate during the last decade (13 per cent compared with 37 per cent during the decade before 1980) may reflect both an increased awareness of the condition and improvements in anaesthetic and surgical management. It is probable, however, that these figures also reflect a bias towards reporting successful cases.

Brisk diuresis, weight loss and prompt reversal of the haemodynamic disturbance were reported in the majority of survivors. Prolonged ventilatory support and/or haemodialysis were required after operation in less than 10 per cent of patients. Other significant complications reported included thrombosis at the site of fistula repair[8,39,64,78], persistent coagulopathy[9], peptic ulceration[13], wound dehiscence[13,72] and anastomotic false aneurysm in the groin[69].

Conclusions and summary of management principles

Without operation, the condition of spontaneous abdominal arteriovenous fistula is invariably fatal. Survival depends on early diagnosis and closure of the fistula with restoration of vascular continuity[22,43]. Delay in diagnosis can lead to inappropriate medical therapy, overtransfusion[12] and aggravation of cardiac failure[9,63]. Once cardiac decompensation has occurred, ventricular function deteriorates rapidly and cardiac failure may become irreversible[9,63].

A clinical diagnosis should be possible in most cases[9]. Although a 'full house' presentation with palpable abdominal aneurysm, machinery murmur, high output cardiac failure and regional venous hypertension is uncommon, being found in less than one-fifth of reported cases, few patients present without at least some signs to suggest a fistula. The diagnosis should be considered in any case of abdominal aneurysm that seems atypical and in any patient with chronic congestive cardiac failure refractory to medical treatment[25]. Confirmation of the diagnosis and localization of the fistula by angiography may be advantageous in a stable patient[17], although it should not delay operation[8].

Occasionally the diagnosis may be missed before surgery, particularly in patients presenting with abdominal aneurysm and cardiovascular collapse. Unexpected haemorrhage from a fistula is an important cause of death in such cases and may be avoided if a diagnosis of threatened or retroperitoneal rupture is routinely reappraised at operation before incision of the aneurysm. Gentle palpation of the aneurysm may reveal a thrill[12,13,32] while pulsating veins[64,72], pulsatile venous bleeding[27,50] and differential wound bleeding[62] are other signs that may alert the surgeon to the presence of an undiagnosed fistula. The anaesthetist may notice paradoxical elevation of the central venous pressure[13] and a routine enquiry by the surgeon will ensure that the significance of this finding is not overlooked.

Gradual clamping of the aorta may be advisable in a stable patient since a sudden increase in cardiac afterload combined with an abrupt fall in venous return may precipitate cardiac arrest[5,50]. Care must be taken during evacuation of the aneurysm thrombus to avoid 'paradoxical' pulmonary embolization[17]. The aneurysm is usually densely adherent to the adjacent vein[26]. Dissection and mobilization of the vein in order to apply clamps or perform a direct repair of the vein wall is therefore both difficult and hazardous[72]. In most cases digital compression of the vein at the site of the fistula will afford sufficient control to permit suture of the fistula from within the aneurysm sac[9], although balloon occlusion catheters should be available[12,89]. Rarely, a large fistula with friable edges cannot readily be sutured and it may be necessary to ligate the inferior vena cava or iliac vein above and below the fistula[32,43]. The operation is completed by routine aortoiliac grafting.

One should anticipate requirement for both ventilatory and inotropic support after operation. Closure of the fistula effectively increases cardiac afterload and vasodilators may be required to protect the already dilated left ventricle. Mobilization of third space fluid may result in a massive diuresis[11,26,43] and significant weight loss[14]. A negative fluid balance should therefore not be corrected without reference to the central venous pressure and haematocrit. Potassium losses must be replaced but a dilutional hyponatraemia is transient and self-correcting. Prophylaxis against venous thrombosis is advisable[58,64,78].

Early diagnosis is the key to successful management of spontaneous abdominal arteriovenous fistula. The classical presentation is, however, uncommon and recognition of this condition relies on a high index of clinical suspicion.

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Use of a metal cannula for peroperative cholangiography

G. S. M. Robertson, B. R. Bullen and A. Gourevitch*

*Department of Surgery, George Eliot Hospital, College Street, Nuneaton CV10 7DJ, and *Queen Elizabeth Hospital, Birmingham, UK*
Correspondence to: Mr B. R. Bullen

Since peroperative cholangiography was first described in 1932[1] it has been shown to reduce the incidence of residual stones in the ducts after cholecystectomy and the number of ducts explored, to provide an idea of the number and location of stones to be retrieved and, by providing anatomical information, may lower the incidence of injury to major structures[2].

These obvious advantages mean that despite recent controversy[3,4] peroperative cholangiography has become widely adopted as a routine part of cholecystectomy[5]. The method used to introduce radio-opaque contrast into the biliary tree is not so standard, but the insertion of a cannula into the common bile duct via the cystic duct appears to be the safest[6]. The range of cannulas described for this purpose includes ureteric catheters, umbilical catheters, infant feeding tubes and the specially designed Stoke-on-Trent cannula and introducer[7]. All of these have the disadvantage of being flexible and awkward to introduce, often impacting on the spiral valve of Heister unless this is gently dilated by a probe, a process that may introduce bubbles of air into the ductal system.

For 25 years surgeons in our area have been using a slightly malleable hollow metal cannula (*Figure 1*). This was adapted from a similar device originally discovered in Denmark. It is now produced by a local firm of surgical instrument makers (Roberts Surgical Healthcare, Kidderminster, UK), and can be connected to a 20-ml syringe by an 80-cm length of transparent plastic tubing (A63 Narrow Bore Extension Set, Avon Medicals, Redditch, UK).

The cannula is designed to act as its own dilator and the olive-shaped end also prevents the inadvertent withdrawal of the cannula from the cystic duct after tightening of the encircling ligature. Its main advantage, however, is the lack of frustration experienced by the surgeon during insertion, which is made easy due to the cannula's rigidity and the 40° bend 15 mm from the end.

The cannula in no way obscures the cholangiogram, has never been known to cause damage to the bile ducts, and can be sterilized for reuse with the other instruments, giving it long-term financial advantages.

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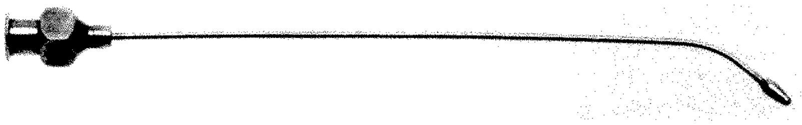

Figure 1 *Photograph showing metal cannula. The cannula is 11·5 cm long*

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Peritoneal adhesion formation after lysis: inhibition by polyethylene glycol 4000

D. O'Sullivan,
M. O'Riordain,
R. P. O'Connell,
M. Dineen and
M. P. Brady

University Department of Surgery, Regional Hospital, Cork, Ireland
Correspondence to:
Mr D. O'Sullivan, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland

Peritoneal adhesions cause much long-term postoperative morbidity. This study evaluates the efficacy of polyethylene glycol (PEG) 4000 in reducing adhesion reformation after lysis. Adhesions were induced, by abrasion, in 111 Sprague-Dawley rats at a first laparotomy. At a second operation, 10 days later, these adhesions were graded and lysed, after which the animals received one of the following solutions intraperitoneally: 5 per cent PEG 4000 ($n=21$)*, 25 per cent PEG 4000* ($n=23$)*, 32 per cent dextran 70* ($n=22$) *or isotonic saline* ($n=25$)*, or were left as an untreated control group* ($n=20$)*. When the reformed adhesions were graded after a further 10 days 5 per cent PEG 4000 was found to be the only solution that inhibited adhesion reformation. The adhesions that reformed in the other four test groups were significantly worse than when they were first graded* ($P \leqslant 0{\cdot}033$ *for all groups). Therefore 5 per cent PEG 4000 may be useful in clinical practice for the reduction of adhesion formation after lysis.*

The prevention of primary formation and reformation of adhesions is central to surgical practice because adhesions are the commonest cause of bowel obstruction: 51 per cent of affected patients in a recent study by Menzies and Ellis[1]. Recurrent adhesive small bowel obstruction is a difficult problem to manage; neither present conservative nor surgical management is consistently effective for either band or widespread adhesions. The commonest operation is 'simple' division of adhesions which is often unsuccessful in the long term because of adhesion reformation. Brightwell *et al.* found a 32 per cent recurrence rate of adhesion obstruction[2]. Adjunctive therapy is required to improve on present results and many auxiliary intraperitoneal agents have been assessed with varying degrees of success[3–13]. Barrier methods, such as Gelfoam® (Upjohn, Kalamazoo, Michigan, USA), Surgicel® (Johnson and Johnson Patient Care Ltd., Ascot, UK) free peritoneal grafts and amnion, which are used to cover traumatized peritoneal surfaces, have been found to increase adhesion formation[3,4]. Various pharmacological and chemical methods have been utilized[4–13] and the most promising to date have been the macromolecules, in particular dextran 70[4–7,9–13]. Most of this experimental work has been directed at the prevention of primary adhesions[4,7,10–12] but, while used frequently by gynaecologists after tubal surgery[6,9,13], dextran 70 has not been consistently effective in preventing adhesion reformation in the clinical context[7,13].

Polyethylene glycol (PEG) 4000 is a macromolecule that has been shown to reduce adhesions when used as a lubricant during insertion of intraocular lenses after phacocystectomy[14]. This relatively non-toxic macromolecule is also widely used as an effective method of bowel preparation before colonoscopy[15,16]. This study investigates the possibility of using PEG 4000 to reduce adhesion reformation after lysis.

Materials and methods

The test solutions used were 5 per cent and 25 per cent PEG 4000 (Abbott Laboratories, Abbott Park, Illinois, USA), 32 per cent dextran 70 (Hyskon; Pharmacia Incorporated, Piscataway, New Jersey, USA) and isotonic saline. PEG 4000 has a molecular weight of 3100–3700 and that of dextran 70 averages 70 000; 5 per cent PEG 4000 is isosmotic with extracellular fluid whereas 25 per cent PEG 4000 is isosmotic with 32 per cent dextran 70, both being hyperosmotic to extracellular fluid. Osmolalities were checked at the beginning of the study by depression of the freezing point method. The doses of PEG 4000 used were 0 6 g/kg and 3 g/kg, both of which are well below the toxic dose in rats of >20 g/kg (Reference 17).

One hundred and eleven male Sprague-Dawley rats weighing 350–450 g (mean weight 395 g) underwent a laparotomy through a 3 cm midline incision under ether anaesthesia. Adhesions were induced by abrading a 4 cm segment of ileum, 10 cm from the ileocaecal valve, five times with a small brush, causing loss of the serosal layer and some petechiae in all animals. Saline (5 ml) was instilled into the peritoneal cavity before closure of the wound

Ten days later all rats underwent a second laparotomy The adhesions that had formed were divided and graded on a scale of 1–4 as previously described by Goldberg *et al.*[8]: grade 1, no adhesions; grade 2, fine filmy adhesions localized to the area of injury; grade 3, dense adhesions requiring sharp dissection but localized to the area of injury; grade 4, widespread adhesions outside the area of initial injury. Before closure of the wound each animal received 5 ml of one of the colourless coded test solutions intraperitoneally or was put in the untreated control group according to a random number system They were thus separated into the following groups 5 per cent PEG 4000 ($n=21$), 25 per cent PEG 4000 ($n=23$), 32 per cent dextran 70 ($n=22$), isotonic saline ($n=25$) and control ($n=20$)

After a further 10 days a third laparotomy was performed on all animals The adhesions that had reformed were divided and graded according to the scheme described above. The effect of each solution on adhesion reformation was determined by subtracting the grade given at the second laparotomy from the final grade given to each animal.

Each of the three stages of the study was carried out by a different operator who was unaware of any previous scores given and solutions used in each animal The Wilcoxon signed rank sum and Mann–Whitney *U* tests were used for statistical analysis.

Results

No rats had adhesions initially and none developed peritonitis. Initial adhesion formation was similar in all groups with no significant difference between them when adhesions were graded at the second operation. Increased, clear intraperitoneal fluid was found at the third laparotomy in 19 out of 44 rats that received PEG 4000 and in seven out of 22 rats that received 32 per cent dextran 70. Excess fluid was not found in either the saline or control groups

The numbers of animals and their adhesion grades at the second and third laparotomies are shown in *Table 1* The 5 per cent PEG 4000 group was the only one in which no animal developed widespread (grade 4) adhesions. The change

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Table 1 *Adhesion grades for each test solution before and after instillation, and the change in individual grade after adhesion reformation*

		Number with each adhesion grade before and after instillation				Change in individual adhesion grade after instillation					
Test solution	Grade	1	2	3	4	−1	0	+1	+2	+3	*P**
5% PEG 4000 ($n=21$)	Before	2	12	7	–	7	11	3	–	–	0 285
	After	7	6	6	–						
25% PEG 4000 ($n=23$)	Before	3	14	6	–	3	11	6	3	–	0 033
	After	2	12	4	5						
32% dextran 70 ($n=22$)	Before	5	12	5	–	3	10	6	3	–	0 033
	After	3	10	6	3						
Saline ($n=25$)	Before	5	14	5	1	2	5	12	1	1	0 007
	After	1	10	10	4						
Control ($n=20$)	Before	2	13	5	–	2	5	10	3	–	0·008
	After	1	6	8	5						

PEG, polyethylene glycol: * Wilcoxon signed rank test

Table 2 *Intergroup comparison of the change in adhesion grading between the second and third operations*

		*P**
5% PEG 4000	*versus* 32% dextran 70	0 04
5% PEG 4000	*versus* saline	0 0035
5% PEG 4000	*versus* control	0·002
25% PEG 4000	*versus* control	0 23
32% dextran 70	*versus* control	0 22

PEG, polyethylene glycol; * Mann–Whitney *U* test

in adhesion grade for each individual rat ranged from a decrease of one grade (−1) to an increase of three grades (+3). The only group in which more animals improved than deteriorated was that with animals treated with 5 per cent PEG 4000, but this trend did not reach statistical significance. It was also the only group in which no animal deteriorated by more than one adhesion grade. In contrast the 32 per cent dextran 70 and 25 per cent PEG 4000 groups had significant deterioration in adhesion grading ($P=0{\cdot}033$ for both groups) The saline and control groups both had an even more marked increase in adhesions after reformation ($P=0{\cdot}007$ and $P=0{\cdot}008$ respectively).

Intergroup comparison of the change in grading that occurred after instillation of the test solutions shows that the 5 per cent PEG 4000 group had a significantly better ($P<0{\cdot}04$) outcome than the other four test groups (*Table 2*). There was no statistical difference in outcome between the 25 per cent PEG 4000, 32 per cent dextran 70, saline and control groups.

Discussion

Peritoneal adhesions are caused by all forms of trauma to the peritoneal surfaces[1,4–6]. The significant increase in adhesions in the control group at each stage of the study underlines the tendency of adhesions to increase with each operation performed[10]. Menzies and Ellis found an incidence of 10 per cent at first laparotomy which increased to 93 per cent at second laparotomy[1]. It is this progressive nature that creates the treatment dilemma in cases of recurrent adhesive bowel obstruction. In the present experiment a change in grade between the second and third laparotomies, or net adhesion formation, was used to assess the effect of each solution to minimize any minor variation that may have existed between groups at the second operation[6,13].

Macromolecules are believed to have three principal modes of action in adhesion prevention. The first is through a prolonged increase in intraperitoneal fluid, due to their oncotic pressure, which floats tissues apart while healing occurs[4–7,10–12]. Their large molecular size ensures that they are absorbed slowly from the peritoneal cavity and thus maintain this tissue separation during the critical time for adhesion formation[11]. Up to 50 per cent of dextran 40 has been shown still to be present intraperitoneally 7 days after its instillation[12]. PEG 4000 is a protein cosolvent causing preferential hydration and stabilization of protein molecules thus creating large, isolated protein–PEG molecules[18] which remain in the peritoneal cavity much longer than would be expected for a molecule of the size of PEG 4000. The finding in this study of increased intraperitoneal fluid in many of the rats given macromolecular solutions, in particular PEG 4000, would lend support to the hydroflotation theory of adhesion inhibition.

The second proposed mode of action of macromolecules is by promotion of non-adherent healing through polymer coating, or 'siliconization', of the injured surfaces[6,7,9]. PEG 4000 could also act in this fashion because its cosolvent activity is increased in the presence of denatured proteins which occur in traumatized areas[18]

Their third proposed action is a direct effect on enzymatic activity which may alter the healing process. Dextran 70 has been shown to alter fibrin structure, making it more digestible to plasmin[9,11]. PEG 4000 also interferes with enzyme activity by altering enzyme structure and creating a hydrophilic shell around the enzyme; this effect is greater on larger enzymes[19] PEG 4000 is much more active in this regard than dextran or povidone[20]. It is interesting to note that while a low concentration of PEG 4000 prevented worsening of adhesions after lysis, the higher concentration of the solution was not effective. This could be explained by the fact that there is a sharp decrease in the preferential hydration of proteins and also destabilization of their structure at higher concentrations due to binding to hydrophobic sites[18]. Direct damage to the peritoneal surface by the hypertonic solution could also be an explanation

While 32 per cent dextran 70 has been found to have some effect in primary prevention of adhesion formation in many species[4,7,10–12] it has been less effective in reducing adhesions after lysis[7,13] and again in this study it has been shown to be without benefit.

Isotonic saline is used, particularly during microsurgical operations, to reduce the incidence of adhesions[9,13] because drying of peritoneal surfaces is a potent stimulant of adhesion formation. This study showed no benefit over controls of using saline at the end of the operation. This is because it neither prevents the drying injury during surgery nor does it remain in the peritoneal cavity during the healing phase because it is absorbed within a few hours

The inconsistent results achieved to date with all adhesion reducing methods have precluded their use as standard therapy in patients having their first laparotomy. Reformation of adhesions was examined in this study because patients suffering from adhesive bowel obstruction or infertility have more to gain from adjunctive therapy. Adhesions were prevented from becoming worse after they had been lysed by using 5 per cent PEG 4000. Before clinical introduction further work needs to be done to determine the therapeutic window for PEG 4000 concentration and to determine if there is any difference in pharmacodynamics when it is given intraperitoneally as opposed to intravenously or orally. Studies also need to be carried out in other animals such as the rabbit and pig to confirm the present results. In conclusion, PEG 4000 could become a useful adjunctive therapy in patients having a second laparotomy.

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Prospective randomized trial comparing anal function after hand sewn ileoanal anastomosis with mucosectomy *versus* stapled ileoanal anastomosis without mucosectomy in restorative proctocolectomy

A prospective randomized trial was performed to compare complications and function after hand sewn ileoanal anastomosis with mucosectomy (group A) with stapled ileoanal anastomosis without mucosectomy (group B) during restorative proctocolectomy. Thirty-two age- and sex-matched consecutive patients under the care of one surgeon were randomized. The median duration of anal dilatation while making the anastomosis was 19 min (range 14–33 min) and 1 min (range 0–39 min) in groups A and B respectively ($P<0{\cdot}005$). *The median level of the anastomosis was at the dentate line (range 0–0·5 cm) in group A and 2 cm above the dentate line (range 0·2–4·0 cm) in group B* ($P<0{\cdot}005$). *Seven patients in group A and 11 in group B had at least one postoperative complication (n.s.). One patient in group A and four in group B developed an anastomotic stricture requiring dilatation (n.s.). One patient in group B had the reservoir removed. Function was assessed at a median of 11 months (range 7–15 months) after ileostomy closure in 14 patients in group A, and at a median of 12 months (range 5–17 months) in 14 patients in group B. Median frequency of defaecation per 24 h was 4 in both groups (group A, range 2–7; group B, range 2–10). Night evacuation (> once per week) occurred in seven patients in each group. All patients in both groups could delay the desire to defaecate by more than 30 min. Eleven patients in group A and 12 in group B had normal continence. Evidence to date favours a full mucosectomy. Function is not vitiated by this technique and surgical removal of the disease is more complete.*

Seow-Choen, A. Tsunoda and R. J. Nicholls

St. Mark's Hospital, City Road, London EC1V 2PS, UK
Correspondence to:
Mr R. J. Nicholls

Restorative proctocolectomy is applicable to large bowel diseases which predominately involve the mucosa. Complete removal is theoretically possible by surgical excision of the colon and most of the rectum and stripping of the mucosa from the anorectal stump. The original technique involved a hand sutured pouch–anal anastomosis following removal of the mucosa of the anorectal stump down to the dentate line. This was regarded as a necessary part of the procedure since it fulfilled the aim of as complete an anatomical removal of the disease as possible[1–3].

There is evidence that the mucosa lining the upper anal canal has useful sensory function[4–8]. It is richly supplied by sensory nerves and may be important in the defaecatory mechanism For this reason, its preservation in restorative proctocolectomy has been recommended[8–11]. Using a stapled anastomosis at the level of the anorectal junction, preserving the transitional zone, it has been claimed that postoperative function is superior to a conventional manual anastomosis combined with a mucosectomy to the dentate line[5,10,11]. This conclusion was drawn from the results of sequentially operated cases raising difficulties in analysis due to learning curve experience and case selection.

The question of anastomotic technique is important since it concerns the extent of removal of the disease. It has recently been shown that severe dysplasia does occur in the anal canal in patients with ulcerative colitis having restorative proctocolectomy and indeed it is the rule with polyposis[12,13]. There may well be a risk of invasion at this site and the functional outcome of one technique over the other would have to be convincingly better for it to be justifiably used.

The results of a prospective randomized clinical comparison of the two anastomotic techniques discussed are analysed to detect differences in the postoperative complication rate, clinical function or physiological variables.

Patients and methods

Thirty-two consecutive patients admitted for restorative proctocolectomy under the care of one surgeon between September 1988 and May 1989 were studied prospectively Patients were stratified for disease status (ulcerative colitis and familial adenomatous polyposis) and all had preoperative anorectal physiology studies including resting and voluntary anal canal pressures, threshold anal sensation to electrical stimulation and functional anal canal length. All patients underwent complete mobilization of the small bowel, total colectomy (if not already done), and protectomy using the close rectal dissection technique. At this point, a sealed envelope was opened, and the patient was randomized to group A or B.

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Group A: Manual anastomosis with mucosectomy

With the rectum completely dissected, a right-angled clamp was placed across the lower rectum. The point of division of the gut tube at about 2 cm above the dentate line was then ascertained by direct vision per anum using an anal retractor After division the length of the anorectal stump above the dentate line was measured with a ruler A W quadruple-limbed pouch was constructed manually in two layers. A mucosectomy was then performed as previously described[1,2], as far distally as a line tangential to the tips of the anal papillae. The reservoir was then brought down to this level and a manual endoanal anastomosis carried out placing interrupted sutures of Polyglactin (20) (Ethicon Ltd., Edinburgh, UK) with minimal anal dilatation. A defunctioning loop ileostomy was constructed.

Total anal dilatation time as well as the total time taken to make the anastomosis was measured with a stop watch. Anastomotic time was defined from the start of mucosectomy to the completion of the anastomosis. The level of the anastomosis with respect to the dentate line was measured.

Group B: Stapled anastomosis without mucosectomy

With the rectum completely dissected to the level of the pelvic floor, a transverse stapling device (Roticulator 30 or 55 stapler, US Surgical Corporation, East Norwalk, Connecticut, USA) was applied 2 cm above the dentate line whenever possible after identification of this point by means of a rectal examination After firing, a right-angled clamp was placed immediately above the staple line, the gut tube divided and the specimen removed. The distance of stapled closure from the dentate line was measured with a ruler. A W pouch was constructed and the detached anvil of the Premium CEEA 31 circular stapler (US Surgical Corporation) was inserted into the distal limb and tied in place using a purse string suture. The shaft of the stapler was introduced per anum and the trochar advanced to puncture the anal stump midway across the transverse staple line The trochar was removed, the anvil in the pouch was inserted and the gun approximated and fired. The 'doughnuts' were inspected and the integrity of the anastomosis checked by palpation and air insufflation. Reinforcing sutures were inserted endoanally if necessary

The total anal dilatation and anastomotic time was measured as in group A. The latter was taken as the time required from the start of the introduction of the purse string suture in the pouch to the point when the instrument was fired, or until the last reinforcing suture had been inserted The level of the anastomosis above the dentate line was measured with a ruler. A defunctioning ileostomy was constructed as in group A.

Postoperative follow-up

All intraoperative difficulties and postoperative complications were recorded All patients were studied at 3-monthly intervals after closure of the ileostomy Clinical assessment was achieved by personal interview and a questionnaire Anorectal physiological function, including resting anal pressure, voluntary contraction, threshold anal sensation to electrical stimulation and functional anal canal length was assessed

Statistical analysis

The results were analysed using the Wilcoxon matched pairs for paired data, the Mann–Whitney test for unpaired data, and the χ^2 test for non-parametric variables.

Results

Patients

Fifteen patients (ten men and five women) were randomized to group A. The median age was 33 years (range 24–47 years). Twelve had ulcerative colitis and three familial adenomatous polyposis. Two patients had had a previous total colectomy, end ileostomy with preservation of the rectal stump, and three had had a previous colectomy and ileorectal anastomosis.

Seventeen patients (eight men and nine women) were randomized to group B. The median age was 33 years (range 16–55 years). Fourteen had ulcerative colitis and two familial polyposis. One patient with ulcerative colitis was ultimately shown to have Crohn's disease after restorative proctocolectomy. Eight had had a previous total colectomy, end ileostomy with preservation of the rectal stump. One patient had had a colectomy with ileorectal anastomosis.

Stapling failed in two patients due to failure of the transverse stapling device in one and the impossibility of its use in the second due to a short anal stump. In the first the stapler jammed and could not be released after firing. A hand sutured anastomosis was necessary. In the other case, a previous removal of the colon and rectum for acute ulcerative colitis had been taken down to the anal canal. This low level of division was not fully appreciated before surgery and there was no possibility of applying a transverse stapler

Operative parameters

The median level of transection of the gut tube above the dentate line was 2·0 cm (range 0·5–3·0 cm) in group A and 2 5 cm (range 0·5–4·5 cm) in group B ($P<0·02$). The median level of the anastomosis was at the dentate line (range 0–0·5 cm) in group A and 2 cm above the dentate line (range 0·2–4·0 cm) in group B ($P<0·005$). Four patients in group B required reinforcing hand suturing of staple line defects.

The median duration of anal dilatation while making the anastomosis was 19 min (range 14–33 min) and 1 min (range 0–39 min) in groups A and B respectively ($P<0·005$). The median time taken to complete the ileoanal anastomosis was 35 min (range 25–45 min) in group A and 25 min (range 15–58 min) in group B (n s.).

Postoperative complications

Seven of 15 patients in group A and 11 of 17 patients in group B had a postoperative complication These were usually minor. Pelvic sepsis related to an anastomotic defect occurred in two patients in group A and three in group B (n.s.). One patient in group A and four in group B required dilatation of an anastomotic stricture (n.s.) One patient in group B developed a pouch–vaginal fistula. All complications are shown in *Table 1*. There was no significant difference in any complication in the two groups.

Clinical function (Table 2)

The median time from restorative proctocolectomy to closure of the ileostomy was 3·5 months (range 1·5–8 months) in group A and 4 months (range 2–10 months) in group B.

In group A, one patient has not had the ileostomy closed for personal convenience and not for a medical indication. There were therefore 14 of 15 patients available for assessment. In group B 14 patients of 17 were assessed, having excluded the single outright failure, and the two protocol failures. The median duration of follow-up from closure of the ileostomy was 11 months (range 7–15 months) in group A and 12 months (range 5–17 months) in group B. The median frequency of defaecation per 24 h was 4 (range 2–7) in group A and 4 (range 2–10) in group B. Night evacuation (defined as the necessity to get up at night one or more times per week) occurred in seven patients in both groups. All patients could defer the desire to defaecate by more than 30 min Eleven patients in group A and 12 patients in group B had completely normal continence

Table 1 *Postoperative complications following restorative proctocolectomy and ileostomy closure*

	Manual (Group A)	Stapled (Group B)
Number of patients	15	17
Number with complications	7	11
Pelvic sepsis		
without anastomotic defect	1	1
with anastomotic defect	2	3
Pouch–vaginal fistula	0	1
Wound infection	1	0
Anastomotic stricture (dilatation needed)	1	4
Intestinal obstruction (laparotomy)		
before ileostomy closure	0	1
after ileostomy closure	1	2
Water/electrolyte loss (ileostomy)	0	2
Failure (excision of reservoir)	0	1

Table 2 *Clinical function after ileostomy closure*

	Manual* (Group A)	Stapled† (Group B)
Number of patients	14	14
Median (range) time from ileostomy closure (months)	11 (7–15)	12 (5–17)
Median (range) frequency of defaecation/24 h	4 (2–7)	4 (2–10)
Night evacuation (> 1 × /week)	7	7
Urgency		
Can wait > 30 min	14	14
Can wait < 30 min	0	0
Continence		
Normal (pad used)	11 (1)	12 (0)
Mucous leak (pad used)	3 (1)	2 (1)
Faecal leak	0	0
Antidiarrhoeal medication	4	2
Ability to discriminate flatus from faeces	8	10
Catheter evacuation	1	0

* Excludes one unclosed ileostomy, † three cases excluded one pouch excised, two failed stapled, *P* not significant for all parameters

Three patients in group A and two in group B had a minor degree of mucous leakage, of which only one patient in each group used a pad. One further patient with completely normal continence in group A used a pad. No patients in either group had any major faecal leakage. Four patients in group A and two in group B required antidiarrhoeal medication. Eight patients in group A and ten patients in group B could discriminate flatus from faeces. One patient in group A required pouch intubation to complete spontaneous evacuation

Physiological variables

In group A the median resting anal pressure fell from 90 cmH_2O (range 60–160 cmH_2O) before the operation to 40 cmH_2O (range 30–80 cmH_2O) after closure of the ileostomy ($P<0{\cdot}005$) (*Figure 1*). Pre- and postoperative median voluntary contraction pressures in group A were 120 cmH_2O (range 80–200 cmH_2O) and 140 cmH_2O (range 70–160 cmH_2O), respectively (n.s.). In group B, the pre- and postoperative median resting pressures were 80 cmH_2O (range 55–200 cmH_2O) and 70 cmH_2O (range 20–100 cmH_2O) ($P<0{\cdot}05$). Respective median voluntary contraction pressures were 100 cmH_2O (range 40–180 cmH_2O) and 160 cmH_2O (range 20–200 cmH_2O) (n.s.). The fall in resting anal pressure after surgery was significantly greater in group A ($P<0{\cdot}02$). There was no correlation between postoperative resting anal pressure and intraoperative anal dilatation time.

The threshold of anal sensation to electrical stimulation was similar in both groups, with a median anal sensation of 3·7 milliamperes (mA) (range 0·8–6·4 mA) in group A and 3·5 mA (range 1·7–4·7 mA) in group B (*Figure 2*). The physiological length of the anal canal was 3·5 cm (range 2·0–4·5 cm) in both groups (*Figure 3*). The distance of the ileoanal anastomosis from the dentate line is shown in *Figure 4*. It was significantly less in the hand sutured group. There were three cases in group B in whom the anastomosis lay more than 3 cm above the dentate line, leaving a short segment of lower rectum behind.

Discussion

Since the introduction of restorative proctocolectomy in the 1970s, several modifications have improved postoperative function. The end-to-end ileoanal anastomosis with the long efferent spout, for example, has been modified or replaced by the side-to-end ileoanal anastomosis, resulting in a marked improvement in spontaneous pouch evacuation[2,14,15]. The long rectal muscular cuff has given way to a short cuff with a decrease in the rate of pelvic sepsis, without a compromise in function[16]. A lower frequency of defaecation has been related to the capacity and type of reservoir[2,14,17].

The most recent modification – to preserve the anal transitional zone[8–11] – has not been tested prospectively despite theoretical advantages. The published evidence demonstrating improved function may be due to other factors such as differences in case selection in consecutive studies, the learning curve in endoanal suturing techniques and the possible damage caused by excessive anal dilatation when using a manual technique[10,14,18–26]. The present study has answered some of these questions. It has the merit of being prospective, randomized and carried out by one surgeon. The results show that there are no obvious differences in complications and that postoperative function is similar whether a hand sutured or stapled technique is used. Any differences in postoperative physiological variables do not appear to affect function.

The differences observed were predictable and included two factors in favour of stapling, a shorter anal dilatation time in the stapled group and a lesser fall in resting pressure after surgery Hand suturing achieved a lower level of anastomosis

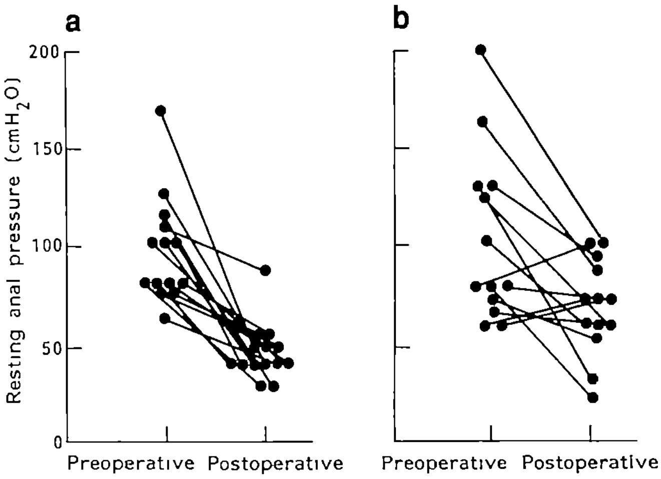

Figure 1 *Relationship between pre- and postoperative resting anal pressures.* **a** *Group A* (n = *14*). *preoperative median 90 cmH$_2$O (range 60–160 cmH$_2$O), postoperative median 40 cmH$_2$O (range 30–80 cmH$_2$O)* (P < *0 005*) **b** *Group B* (n = *13*) *preoperative median 80 cmH$_2$O (range 55–200 cmH$_2$O); postoperative median 70 cmH$_2$O (range 20–100 cmH$_2$O)* (P < *0 05*)

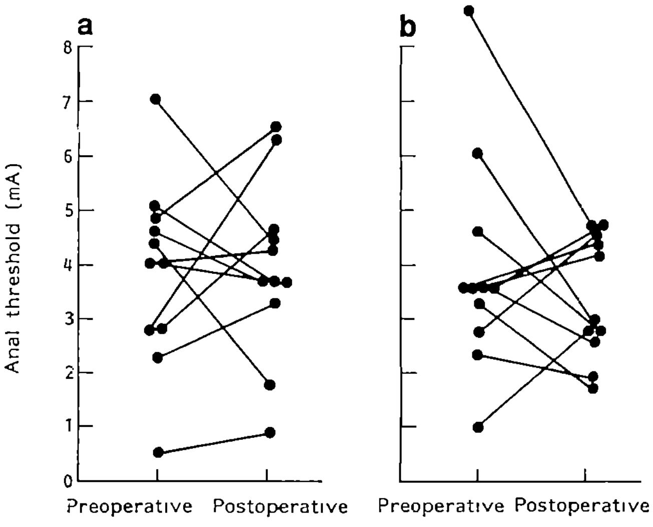

Figure 2 *Relationship between pre- and postoperative threshold of anal sensation to electrical stimulation.* **a** *Group A* (n = *11*) *preoperative median 4 0 mA (range 0·5–7·0 mA); postoperative median 3·7 mA (range 0 8–6 4 mA)* (P = *n.s.*) **b** *Group B* (n = *11*)· *preoperative median 3·5 mA (range 1·0–8·9 mA), postoperative median 3·5 mA (range 1 7–4 7 mA)* (P = *n s*)

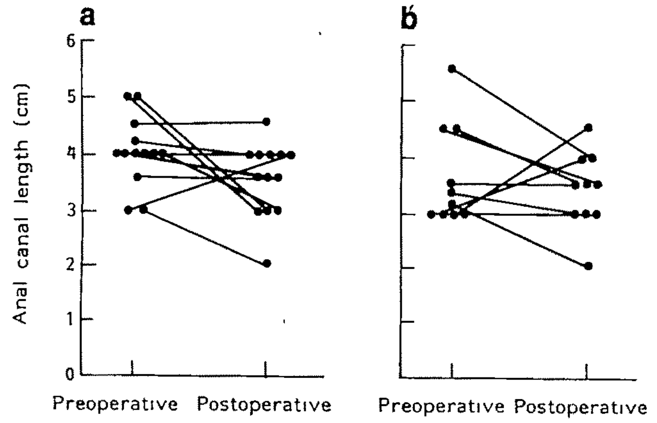

Figure 3 *Relationship between pre- and postoperative physiological anal canal length* **a** *Group A* (n = *13*) *preoperative median 4·0 cm* (*range 3·0–5·0 cm*)*; postoperative median 3·5 cm* (*range 2·0–4·5 cm*) (P = *n.s.*). **b** *Group B* (n = *10*) *preoperative median 3·3 cm* (*range 3·0–5·5 cm*)*, postoperative median 3·5 cm* (*range 2·0–4·5 cm*) (P = *n.s.*)

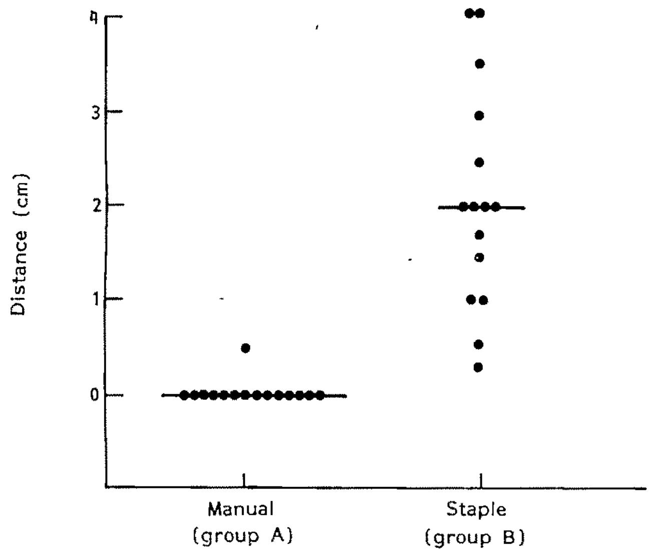

Figure 4 *Scattergram showing the distance of the ileoanal anastomosis above the dentate line Group A. median 0 cm* (*range 0–0·5 cm*)*. Group B: median 2 cm* (*range 0·2–4 cm*) (P < *0·005*)

in relation to the dentate line. This had more than theoretical importance since three cases in group B had a significant amount of lower rectum left after stapling. Even if the cancer risk is small, persistent inflammation might well continue to cause local symptoms[11]. In these three cases it was technically difficult to get the transverse stapler down to the level of the anorectal junction owing to a narrow pelvis. In addition, there were the two technical failures in the stapled group, both of which had to be salvaged by hand suture. Four further cases in group B required the insertion of sutures manually to augment defects left by stapling. The pouch–vaginal fistula in group B was the first encountered by the authors in over 350 cases of restorative proctocolectomy. It may be that the double staple technique predisposes to this. This complication is important since it is difficult to correct[27,28].

These experiences emphasize that stapling should not be used by a surgeon who is not also competent in the technique of hand suture. The operation is a specialist procedure and if all goes well the patient is delighted, avoiding morbidity and a permanent stoma

The physiological data have shown no difference in voluntary contraction pressure in the anal canal, no difference in the functional anal canal length, and no difference in anal sensation as ascertained by electrical stimulation. These results are concordant with the similar clinical function, particularly of continence and the ability to discriminate faeces from flatus in the two groups. If the transitional zone has useful function in theory, it does not appear to be greatly important in practice. The fall of resting pressure in almost every case in the hand sutured group did not adversely influence function. Of interest, and perhaps unexpectedly, was the observed fall in resting pressure in many of the patients in the stapled group and this, despite a minimal anal dilatation time. The protocol of the study did not include measurements of pouch capacitance and data on the volumes within the reservoir that lead to the desire to defaecate are not available. Long-term monitoring of reservoir and anal canal pressures was not carried out and it is therefore impossible to comment on the sampling reflex in the patients in the study.

The possible risk of leaving diseased lower rectal mucosa behind has been highlighted recently. Persistent inflammatory symptoms including bleeding have been reported when diseased mucosa has been retained[11]. The anal mucosa in 16 patients having a restorative proctocolectomy for ulcerative colitis showed moderate dysplasia in four and an unsuspected adenocarcinoma in one[13]. In a larger study we found dysplasia in the anal mucosa in three of 118 colitic patients. While this was a low prevalence, two of the three cases were in patients who had a coincidental carcinoma in the large bowel. In polyposis almost all patients (12 of 14) had dysplasia in the anal strippings[12].

The evidence to date favours a full mucosectomy. Function is not vitiated by this technique and surgical removal of the disease is more complete

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1,25-Dihydroxyvitamin D_3 receptors and human colon adenocarcinoma

P. Lointier, F. Meggouh*, P. Dechelotte†, D. Pezet, Ch. Ferrier, J. Chipponi and S. Saez*

*Service de Chirurgie Générale et Digestive, Hôtel-Dieu, B P. 69, 63003 Clermont-Ferrand, *Service de Biologie Médicale, Centre de Lutte contre le Cancer Léon Bérard, 28 rue Laennec, 69373 Lyon Cedex 08 and †Laboratoire d'Anatomie Pathologique, Hôtel-Dieu, B P. 69, 63003 Clermont-Ferrand, France*

Correspondence to:
Professor P. Lointier

Epidemiological evidence suggests that dietary calcium and 1,25-dihydroxyvitamin D_3 *(1,25-*$(OH)_2D_3$*) might have a protective effect against colorectal cancers. Since the presence of receptors is required for steroid action, specific 1,25-*$(OH)_2D_3$ *receptors (*RD_3*) were investigated in biopsies taken at different levels of the colon. The study involved 90 biopsies from patients operated on for colorectal adenocarcinoma. They were paired biopsies from adenocarcinoma tissue and adjacent normal mucosa. In addition, 26 normal intestinal mucosa biopsies from patients without cancer were examined.* RD_3 *receptors were assayed in tissue extract by the dextran-coated charcoal technique and also characterized by sucrose density gradient sedimentation. Scatchard analysis showed a single class of specific high affinity–low capacity sites binding for 1,25-*$(OH)_2D_3$*. The incidence of* RD_3 *was 86 per cent in normal mucosa* ($n = 77$) *and lower in carcinoma* ($n = 34$)*, for which the incidence decreased significantly* ($P < 0{\cdot}001$) *from right colon (58 per cent) to left colon (37 per cent) and rectum (19 per cent). These data suggest that the normal colon is a potential target organ for 1,25-*$(OH)_2D_3$ *which might modulate calcium transport in the colon. Loss of receptivity to 1,25-*$(OH)_2D_3$ *is associated with malignant transformation.*

While colorectal cancer is one of the commonest tumours observed in Western populations, little is known of the mechanisms controlling the development of this disease. Antineoplastic activity has been proposed for both vitamin D and calcium[1–7]. Garland and Garland[2] were the first to propose that vitamin D might afford protection against colon cancer, reporting that colon cancer mortality rates were highest in places where populations were exposed to the least amounts of natural light. Another epidemiological study determined the relative risk of colon cancer due to milk consumption to be 0·3, suggesting a protective effect of vitamin D-fortified milk.

An essential role of the active metabolite 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) has been described in the regulation of extracellular calcium homoeostasis. 1,25-$(OH)_2D_3$ appears also to be a modulator of growth and differentiation of various kinds of neoplastic cells[8–15] We previously demonstrated the existence of 1,25-$(OH)_2D_3$ receptors (RD_3) in the human colon cancer cell line LOVO[11], and reported the association of growth reduction with a more differentiated phenotype after 1 week of treatment. The differentiation stages also have been related to the receptor level[12] in the human colon cancer cell line HT29.

The data available on RD_3 concern only colon cancer cell lines. Whether or not normal colonic epithelial cells and primary colon tumours express RD_3 has not been ascertained. Since the steroid hormone is known to act through a receptor-activated genomic process[13], the status of RD_3 in human colorectal tumours and in the corresponding normal mucosa were investigated in the present work.

Material and methods

Chemicals

1,25-$(OH)_2$ [26,27-methyl^{3}H]-cholecalciferol (176 Ci/mmol, specific activity) with a radio purity of 98·4 per cent was obtained from Amersham, France Inert 1,25-$(OH)_2D_3$ was a generous gift from F Hoffmann La Roche and Co. Ltd , Basel, Switzerland It was prepared as pure ethanol solution (10^{-3} M) and stored under nitrogen in amber vials at −20°C. Aprotinin and bovine serum albumin (BSA) were from Sigma, France. All other reagents were purchased from Merck, Germany.

Tissue collection

Adenocarcinoma and distant (5–10 cm) adjacent normal mucosa were obtained at the time of surgery from 90 patients operated on for colorectal cancer. Fresh samples were rinsed with cold isotonic buffer solution and immediately stored in liquid nitrogen until assay 1–3 weeks later. No patient had received chemotherapy or radiotherapy before operation.

Pathology reports were used to determine the degree of extension of the lesion in the intestinal wall and the presence of lymph node metastases. Each lesion was staged by the Dukes' classification for carcinoma of the colon and rectum[16] In addition eight duodenal and small bowel and 18 normal large bowel mucosa biopsies were obtained from non-tumour-bearing patients operated on for digestive ulcer, sigmoiditis or submitted to digestive surgery after abdominal trauma.

Cytosol preparation and receptor binding

The frozen tissues were pulverized into fine powder with a cryogrinder (Cryorivoire, Montpellier, France) and the cytosol was prepared by suspending the tissue powder in buffer PEMDK (25 mM KH_2PO_4, 1·5 mM EDTA, 10 mM Na_2MoO_4, 1 mM DTT, 300 mM KCl and 0·6 units of the protease inhibitor aprotinin) Homogenization was done with 4–6 strokes of 5 s in a polytron PT-10 (Kinimatica, GMBM, Switzerland) and the mixture was maintained at 4°C in ice with frequent agitation for nuclear receptor extraction Cytosols were then prepared by ultracentrifugation at 105 000*g* at 4°C for 60 min Clear supernatants were removed from beneath the fatty layer. Cytosol protein concentration was determined by the method of Lowry[17]. The cytosol was diluted to 0·1 M KCl with PEMD (PEMDK without KCl) before binding incubations.

RD_3 were determined by incubating cytosol aliquots with [^{3}H]1,25-$(OH)_2D_3$ at increasing concentrations from 5×10^{-11} M to 10^{-8} M. Non-specific binding was assessed by duplicate samples with a 100-fold excess of inert ligand. The samples were incubated at 4°C for 16 h Unbound 1,25-$(OH)_2D_3$ was removed by dextran-coated charcoal (DCC) in PEMD (0 1 per cent w/v) treatment at 4°C for 10 min under constant stirring. The DCC was pelleted by centrifugation at 2500*g* for 10 min.

The radioactivity in the supernatant was then counted in a

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Table 1 *Clinical characteristics of the 90 patients operated on for colorectal adenocarcinoma*

Clinical features	Right colon ($n=31$)	Left colon ($n=27$)	Rectum ($n=32$)	Significance
Sex				
M	18	18	19	$\chi^2=0·32$
F	13	9	13	(n.s.)
Differentiation status				
Well	15	14	20	$\chi^2=1·34$
Moderate and poor	16	13	12	(n.s.)
Dukes' classification				
A+B	15	10	20	$\chi^2=3·84$
C+D	16	17	12	(n.s.)

n.s., Not significant; *n*, number of adenocarcinomas

Table 2 *1,25-Dihydroxyvitamin D_3 receptor (RD_3) levels in small bowel normal mucosa from non-cancer-bearing patients*

Sex	Age (years)	Site	RD_3 level (fmol/mg protein)	K_d ($\times 10^{-10}$ M)
F	37	Ileum	38·4	3·4
F	44	Ileum	41·0	6·6
F	78	Ileum	0	
M	44	Ileum	39·0	8·7
M	62	ileum	75·7	3·8
M	57	Ileum	13·7	3·8
M	59	Ileum	25·5	4·1
F	66	Duodenum	42·7	2·7

K_d, equilibrium dissociation constant

scintillation counter. Receptors were expressed as bound 1,25-$(OH)_2D_3$ fmol/mg cytosol protein.

Sucrose density gradient sedimentation

Cytosol aliquots were incubated with $[^3H]1,25\text{-}(OH)_2D_3$ at a final concentration of 10^{-9} M, with or without 100-fold excess of unlabelled ligand. Incubations and DCC treatment were as in the binding assay. Aliquots were layered on the top of a linear 5–20 per cent (w/v) sucrose density gradient prepared in PEMD containing 0·1 M KCl and sedimented at 300 000*g* in a vertical rotor (Sorvall) for 3 h. BSA was used as density marker. Five-drop fractions were collected from the bottom of the tube and their radioactive content determined.

Statistical analysis

The χ^2 test was used for the comparison of distribution and percentages. Means were compared by the ε test for paired data, the Student's *t* test for small population samples where variances were equal, and the Mann–Whitney *U* test for small population samples where variances were unequal. The Fisher *F* test was used for variance comparison.

Results

Ninety matched normal/tumour pairs of biopsies from patients with sporadic colon carcinoma were examined for the presence of RD_3. The clinical characteristics of the 90 patients treated surgically for colorectal adenocarcinoma are shown in *Table 1*. In this group the distribution of the biopsies in the three main colonic localizations was no different with respect to sex, differentiation status and extension of the disease as defined by the Dukes' classification. Of the 90 patients, 55 were men with a median of age 65·5 years (range 35–89) and 35 were women with a median of age 67·6 years (range 41–89).

Evidence of RD_3 was found in seven of eight samples obtained from small bowel mucosa and 15 of 18 samples obtained from large bowel mucosa of non-cancer-bearing patients (*Tables 2* and *3*). In cancer-bearing patients RD_3 were detected in the majority of normal mucosa biopsies: 77 out of 90 (86 per cent) were RD_3-positive (*Table 4*). RD_3 incidence did not differ with biopsy location, age or sex. *Table 5* shows the incidence and the distribution of RD_3-positive specimens from carcinomas classified on the basis of the characteristics outlined in *Table 1*.

The RD_3 incidence in normal mucosa was 86 per cent and in carcinoma was 37 per cent (34 of 90), decreasing from the right colon (58 per cent) to the left colon (37 per cent) and the rectum (19 per cent). Statistical analysis of these distributions indicates that the incidence of RD_3 varies in relation to tumour localization along the digestive tract. It is significantly higher in right colon than in rectal tumours ($P<0·001$). There was no

Table 3 *K_d and number of 1,25-dihydroxyvitamin D_3 receptors (RD_3) in normal human colon biopsy specimens from non-cancer-bearing patients*

Site	Sex	Age (years)	RD_3 level (fmol/mg protein)	K_d ($\times 10^{-10}$ M)
RC	M	59	107·0	1·60
RC	W	78	16·6	1·07
LC	M	71	48·7	0·36
LC	W	63	71·0	1·18
LC	M	50	20·6	0·60
LC	W	59	81·0	1·08
LC	W	77	76·8	0·38
LC	M	78	0	ND
LC	M	51	0	ND
LC	M	58	9·8	0·50
LC	W	64	43·8	0·49
LC	W	63	0	ND
LC	M	64	45·0	0·56
LC	M	66	30·8	0·57
LC	M	55	43·3	0·85
LC	W	39	33·3	0·62
LC	M	65	36·0	1·25
LC	W	44	51·3	2·60

RC, right colon; LC, left colon; ND, not detected, K_d, equlibrium dissociation constant

Table 4 *Incidence of 1,25-dihydroxyvitamin D_3 receptors (RD_3) in normal mucosa of 90 cancer patients*

	Sex		Right colon	Left colon	Rectum	Total
	F	M				
RD_3-positive	30	47	28	20	29	77
RD_3-negative	5	8	3	7	3	13
	$\chi^2=0$ (n.s.)			$\chi^2=3·80$ (n.s.)		

n.s., Not significant

Table 5 *Distribution of 1,25-dihydroxyvitamin D_3 receptors (RD_3) in 90 patients with adenocarcinoma*

Clinical features	RD_3-positive ($n=34$)	RD_3-negative ($n=56$)	Significance
Tumour site			
Right colon	18 (58)	13 (42)	$\chi^2=10·33$
Left colon	10 (37)	17 (63)	$P<0·01$
Rectum	6 (19)	26 (81)	
Dukes' classification			
A+B	14	31	$\chi^2=1·7$
C+'D'	20	25	n.s.
Differentiation grade			
Well	20	29	$\chi^2=0·4$
Moderate and poor	14	27	n.s.
Sex			
M	22	33	$\chi^2=0·2$
F	12	23	n.s.

Values in parentheses are percentages, n.s., not significant

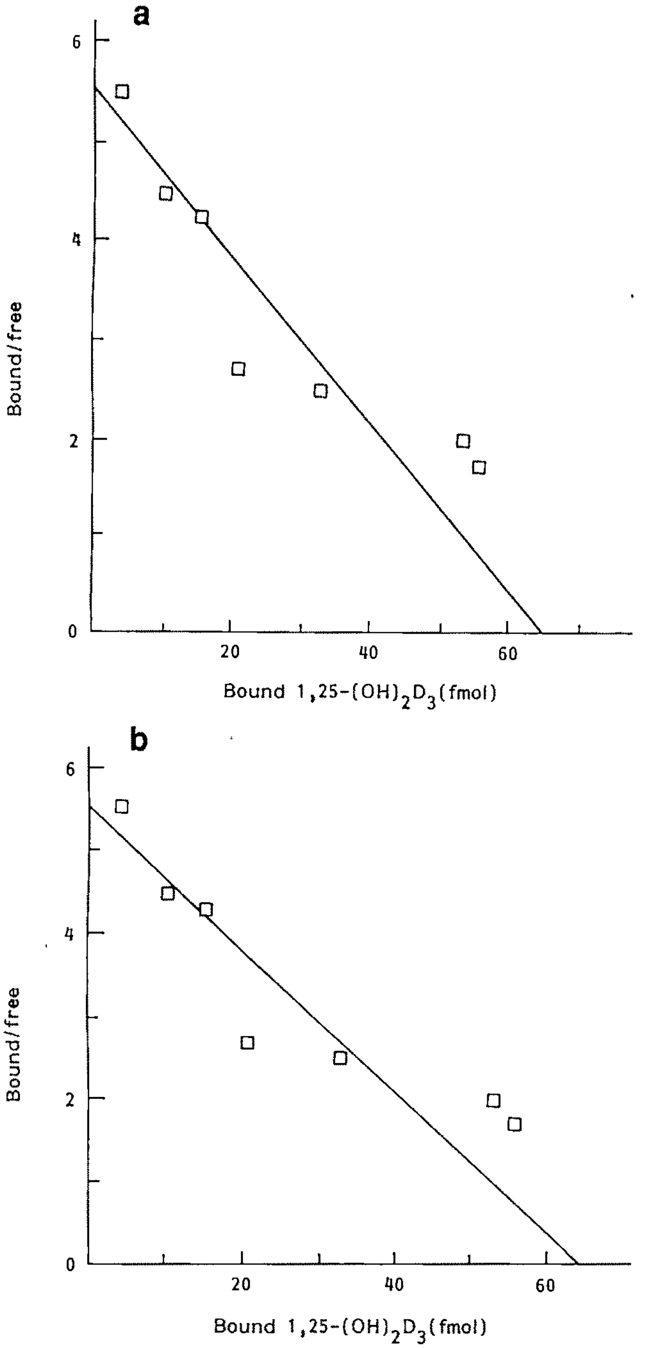

Figure 1 *Scatchard analysis of specific [^3H]1,25-(OH)$_2$D$_3$ binding to cytosols from* **a** *normal colon mucosa and* **b** *the corresponding tumour. Cytosols were incubated as indicated in the text Each point represents the mean of three determinations*

correlation of the presence or absence of RD$_3$ with age, sex, Dukes' stage or histological grade.

The value of receptor content did not significantly differ between RD$_3$-positive biopsies, whatever their nature, maligant or not. Assays in different parts of the same tumour revealed no heterogeneity of the receptor distribution (data not shown). The mean(s.e.m.) values in normal mucosa and carcinoma were 80·2(60·8) fmol/mg protein and 73·2(51·4) fmol/mg protein respectively. The receptor content in normal mucosa and carcinoma was not significantly different from that in biopsies from non-tumour-bearing patients (Mann–Whitney $U = 0{\cdot}47$ and 0·48 respectively).

Scatchard analysis of binding data obtained from the biopsies indicated the existence of a single class of high affinity binding sites. The mean(s.e.m.) values of the equilibrium dissociation constant (K$_d$) for normal mucosa and carcinoma were $1{\cdot}66(0{\cdot}91) \times 10^{-10}$ M and $1{\cdot}62(0{\cdot}84) \times 10^{-10}$ M respectively (*Figure 1*).

The sedimentation coefficient of the RD$_3$ complex prepared in hypertonic buffer (PEMD, 0·3 M KCl) was approximately 3·2 S (*Figure 2a*). The radioactivity was associated with a single peak which was totally quenched in samples incubated in the presence of an excess of inert ligand No radioactive peak was observed in tumour samples which did not display specific binding by Scatchard analysis (*Figure 2b*). Findings were similar when using samples from different sites along the colon and the rectum (data not shown).

Discussion

The present work demonstrates the presence of RD$_3$ in the colorectal epithelial cells The biochemical characteristics of the RD$_3$ are similar to those of the intestinal small bowel receptors

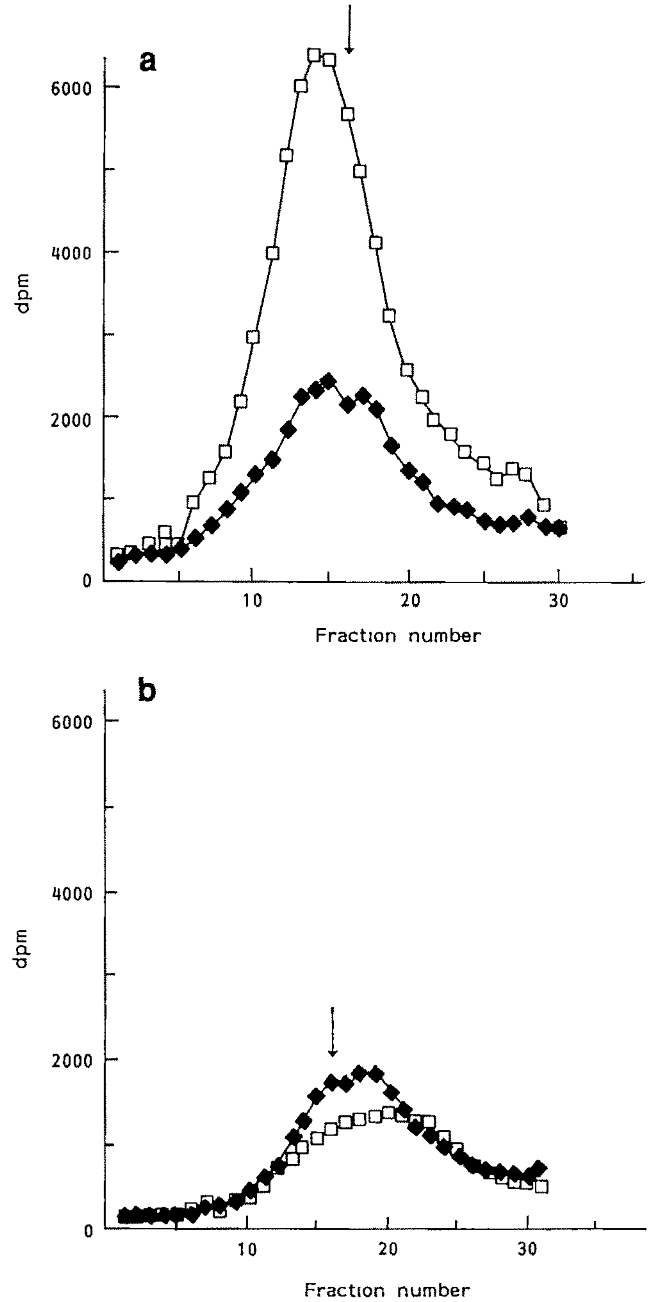

Figure 2 *Sucrose density gradient sedimentation analysis of [^3H]1,25-(OH)$_2$D$_3$ binding in the presence (◆) or absence (□) of a 100-fold excess of unlabelled [^3H]1,25-(OH)$_2$D$_3$ in* **a** *colonic mucosa and* **b** *adenocarcinoma cytosols Arrows show sedimentation of bovine serum albumin dpm, disintegrations per min*

for 1,25-$(OH)_2D_3$ (References 13 and 18). This is established by ligand specificity, binding affinity, and by sucrose density gradient sedimentation. The dissociation constant and sedimentation coefficient are similar to those of recent studies using human, chick and rat intestine[19–21]. These findings show that the human colon might be a potential target organ for 1,25-$(OH)_2D_3$ and suggest that 1,25-$(OH)_2D_3$ could play a role in phosphate and calcium homoeostasis regulation In favour of this hypothesis, the recovery of calcium absorption by colonic epithelium is observed after small bowel resection, and is associated with morphological changes[22]. In the ascending colon, the calcium absorption may become comparable with that for the duodenum[23–25] and may be increased by adding 1,25-$(OH)_2D_3$

It may be suggested that 1,25-$(OH)_2D_3$ plays a role in these modifications of colonic activity and morphology, both being mediated by the corresponding receptors. Moreover, the cytosolic calcium binding proteins are positively regulated by 1,25-$(OH)_2D_3$. These normally participate in calcium ion exchanges in the brush border cells of the small intestine; they are also present at detectable levels in mucosa samples of colon from patients with severe short bowel syndrome[26]

The present investigation, which demonstrates the presence of RD_3 over the whole length of the bowel, implies that the human colon is involved in calcium absorption which is clinically significant and regulated by 1,25-$(OH)_2D_3$, especially in the right colon. Another major aspect of these findings concerns the pathophysiology of colorectal cancer. The general incidence of RD_3 is lower in carcinoma than in normal mucosa biopsies and is at variance with its frequency in colon cell lines[11,27,28]. This could be related to special selection of RD_3-positive cells during the establishment of the lines. Nevertheless, the present data provide clear evidence of the disappearance of 1,25-$(OH)_2D_3$ binding capacity in tumour *versus* normal colorectal mucosa. There is concordance between the presence of RD_3 and a well-differentiated morphology, as observed in a preliminary study[29,30], while a similar correlation is not observed in tumour cell line after *in vitro* differentiation[12] The modulation of RD_3 might be dependent on the degree of differentiation and be restricted to specific functional stages in the physiology of normal and tumour cells.

Antiproliferative effects of 1,25-$(OH)_2D_3$ on tumour cells have been observed. These may include inhibition of the growth of xenografts derived from colonic human cell lines in immunodepressed mice[8] or growth reduction of other lines *in vitro*[9–11]. Other experimental studies suggest a protective role of 1,25-$(OH)_2D_3$ against the promotion of chemically induced colon cancer[31,32]. In such experimental conditions the 1,25-$(OH)_2D_3$ activity would apparently take place at an early stage of carcinogenesis. It could be limited to the membrane and intracellular calcium ion exchanges which are involved both in the growth factor receptor and specific functional activities.

On the basis of this prospective evaluation of 90 patients, the absence of difference in the incidence of RD_3 in normal mucosa taken from non-tumour-bearing patients and that observed in normal mucosa biopsies suggests that there is no RD_3 lesion preceding colon carcinogenesis which favours its promotion. The different incidence of these receptors in normal mucosa and carcinoma biopsies suggests that the loss of receptors could be related to an alteration of the gene expression associated with the neoplastic process. No benefit should be expected from treating tumours which do not contain RD_3 with 1,25-$(OH)_2D_3$. Whether the active metabolite of vitamin D_3 or synthetic analogues may influence carcinoma cells *in vivo* remains to be seen. This cohort of patients will be followed so that the longer term prognosis related to RD_3 levels can be determined. However, this demonstration of the presence of RD_3 in some adenocarcinomas of the colon should encourage further investigations of the effect of 1,25-$(OH)_2D_3$ on colorectal carcinogenesis. The functional response to 1,25-$(OH)_2D_3$ of both human colon cancer cell lines *in vitro* and experimental models of colonic cancer may be relevant to these clinical studies

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Prevention of anastomosis leakage: an artificial connective tissue

J. F. Marescaux,
M. Aprahamian*,
D. Mutter, E. Loza,
M. Wilhelm, P. Sonzini
and C. Damge*

Service de Chirurgie Digestive,
Université Louis Pasteur,
*Strasbourg and *Unité de*
Recherche, 61 de l'INSERM,
Strasbourg, France
Correspondence to:
Dr J Marescaux, Clinique
Chirurgicale A, Hôpital Central,
67091 – Strasbourg Cedex, France

Anastomosis leakage still causes considerable morbidity and mortality after digestive tract surgery. We report here our experience of the use of reconstituted connective tissue created from elastin, fibronectin and collagen in preventing anastomosis leakage and closing intestinal fistulas. In animal studies (56 rats), this connective tissue was used as a patch applied with fibrin sealant to the edges of a 1 cm diameter colonic defect. In a clinical evaluation, eight patients had an intestinal fistula closed by a simple sewn suture reinforced by a sealed patch and seven patients had a high risk anastomosis reinforced by a sealed patch, in most cases as an alternative to staged surgery. In animal studies, complete reconstitution of the three colonic layers was obtained without retraction and without inflammatory reaction within 40 days, while the patch was slowly resorbed. In clinical trials all 15 defects and anastomoses healed without complication. Three patients died from other causes and, at autopsy, the patch was found to have remained in place covering the suture line. If these results are confirmed by a prospective clinical trial, such biomaterial offers the possibility of reducing the occurrence of anastomosis leakage, especially in high risk circumstances.

Postoperative anastomosis leakage is a major complication of digestive tract surgery. Gastrointestinal fistulae continue to cause significant morbidity and mortality in spite of improved preoperative care and the availability of new operative closure techniques such as stapling and fibrin-based biological glues. None of these techniques has significantly improved anastomosis leakage rates to date, and this led us to investigate a novel approach to preventing anastomotic failure and aiding fistula closure. Aware of the recent advances in the use of *in vitro* reconstituted matrices as biological supports for cell cultures as well as the increased frequency of their use in other surgical specialities, we considered that such reconstructed connective tissue might be of value in gastrointestinal surgery. The first stage of study consisted of adapting the biomaterial to comply with the specific needs of gastrointestinal surgery. The second stage examined healing of a colon defect covered by the biomaterial in rats. The results obtained from these animal studies enabled us to undertake a third stage to adapt the biomaterial so that it could be used as a protective support of healing wounds in man and in the repair of digestive tract fistulae where conventional treatment had little chance of success or had already failed.

Materials and methods

Preparation of artificial tissue and fibrin sealant

The reconstituted connective tissue matrix was prepared as previously described[1,2]. The elaboration of this material results from the combination of two chemical reactions The first is the formation of a covalent bond between elastin – a major component of connective tissue – and soluble fibrin monomers generated by thrombin, yielding an addition product or adduct The second reaction is due to a Ca^{2+}-dependent affinity of fibronectin for elastin

The synthesis of the final product, by adding fibronectin and collagen to the components of the adduct, was performed as follows. Lyophilized powder of cold insoluble proteins (CRTS, Strasbourg, France) was dissolved at 37°C with 6 ml phosphate buffer, pH 7·4 The solution containing 40 g/l of fibrinogen and 7 g/l of fibronectin remains stable at room temperature and can be stored for 1 week at 4°C. To 100 mg of bovine neck elastin (Elastin Products Company Pacific, Missouri, USA), or 100 mg of human aortic elastin, 0·5 ml of cryoglobulin solution was added and mixed. At that time other ingredients such as 0 1 ml (1000 international units) of Zymofren® (Specia, Paris, France), 1 ml of soluble collagen (3 mg of type I collagen) and thiourea (1 mg) were added. Finally, thrombin (6 units) was added during stirring The mixture was immediately poured into a mould of predetermined shape and kept for at least 30 min at 37°C before withdrawal. Excess buffer was removed using blotting paper and the sample was kept until use in a sanitized package after γ-ray sterilization (2500 cGy)

The synthesis of the two-component fibrin sealant (Transglutine®, Centre Régional de Transfusion Sanguine de Strasbourg, France) exploits the final stage of the coagulation process. The main component is human fibrinogen obtained by cryoprecipitation together with fibronectin and factor XIII which is known to stabilize the fibrin polymers (the clot). Aprotinin was added to protect the sealant from plasmin activity. The second component is lyophilized equine thrombin reconstituted in a $CaCl_2$ solution. The cohesive elastic sealant, adhering to adjacent tissue by physical forces and chemical bonds, was tightly stuck in 3–5 min.

Animal studies

Fifty-six adult ether-anaesthetized Wistar rats weighing 250–350 g were used A median laparotomy was performed, the caecum exposed and a 1 cm diameter piece of tissue removed from the anterior surface Reference sutures (Prolene 6/0, Ethicon, UK) were placed at 5 mm intervals around the wound edge to assure haemostasis and serve as reference points during healing. A 15 mm wide, 2 mm thick patch was applied to the wound using the fibrin sealant previously described (*Figure 1a*). The adhesion of the patch controlled, the caecum was replaced and the skin incision closed Ten of the rats served as a control group in that a 1 cm diameter hole was created on the caecum without suturing, and covered with omentum

Groups of eight animals were killed on postoperative days 5, 10, 15, 20, 30, 40 and 60. In the macroscopic examination, the abdominal cavity was explored for abscesses or adhesions. The exterior of the patch was observed, and the caecum was opened for examination of the interior face of the scar area. The operated area was excised for histological study

For scanning electron microscopy, samples were fixed in 2 per cent glutaraldehyde for 48 h at 4°C, dehydrated in graded series of ethanol, then transferred in isoamylacetate and dried at the critical point. A

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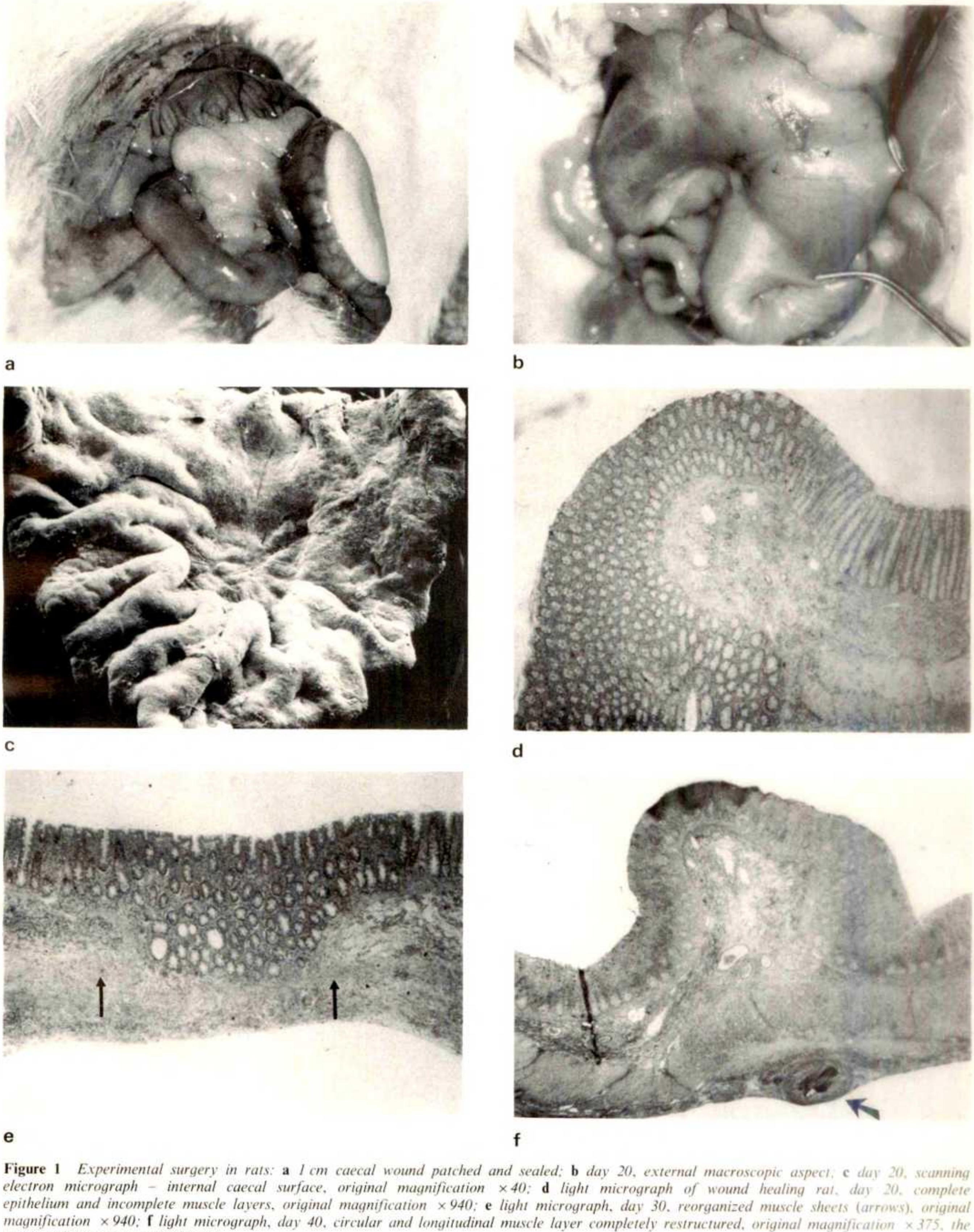

Figure 1 *Experimental surgery in rats:* **a** *1 cm caecal wound patched and sealed;* **b** *day 20, external macroscopic aspect;* **c** *day 20, scanning electron micrograph – internal caecal surface, original magnification ×40;* **d** *light micrograph of wound healing rat, day 20, complete epithelium and incomplete muscle layers, original magnification ×940;* **e** *light micrograph, day 30, reorganized muscle sheets (arrows), original magnification ×940;* **f** *light micrograph, day 40, circular and longitudinal muscle layer completely restructured, original magnification ×375, the arrow indicates the residual patch*

15 nm thick layer of gold was deposited on the samples. Samples were examined in a Philips 501 B (Eindhoven, The Netherlands) scanning electron microscope operated at 20 kV.

Light microscopic studies were done on samples fixed in Susa of Heidenhain's solution for 48 h at 4°C and dehydrated in ethanol. Paraffin sections were stained with orcein.

Clinical evaluation

Fifteen patients were fitted with elastin patches. Agreement was given for clinical trial by the Hospital Ethical Committee. The eight patients in group 1 presented with a digestive tract fistula for which conventional treatment had been unsuccessful or could not be envisaged. In these patients, the patch was added to reinforce a sewn suture performed

Table 1 *Details of patients in group 1*

	Diagnosis	Conventional approach before patch application	Treatment with patch	Results
Case 1 53 years	Leakage from cervical oesophagogastric anastomosis after oesophagectomy for cancer	Two reoperations: – excision of edges and suture – myoplasty	Excision of edges Sewn suture Sealed patch	Low output fistula for 6 days – clinical, radiological and endoscopic evidence of complete healing at 15th postoperative day
Case 2 55 years	Two exposed fistulae of the small bowel following evisceration	—	Excision of edges Sewn suture Sealed patch	Good healing of one fistula (clinical evidence) Recurrence of the other fistula because of early lysis of the patch attributed to local excessive fibrinolysis (clot covering patch)
Case 3 76 years	Rectovesical fistula after anterior resection of the rectum for cancer	Two reoperations: – excision of edges – separate sewn suture of rectum and bladder	Excision of edges Separate sewn suture of bladder and rectum Interposed sealed patch	Good healing (clinical, radiological and endoscopic evidence)
Case 4	Rectovaginal fistula after anterior resection of the rectum for cancer	Two reoperations: – excision of edges – separate sewn suture of rectum and vagina	Excision of edges Separate sewn suture of rectum and vagina Interposed sealed patch	Good healing (clinical, radiological and endoscopic evidence)
Case 5 61 years	Leakage from an ileotransverse anastomosis after right hemicolectomy for cancer	—	Excision of edges Sewn suture Sealed patch	Good healing (radiological evidence)
Case 6 70 years	Duodenal fistula involving prosthetic aortic aneurysm	—	Excision of edges Sewn suture Sealed patch	Death at day 6 postoperatively Autopsy: peritonitis due to ischaemic perforation distal to the previous fistula The patch was in place covering the previous fistula
Case 7 56 years	Leakage from duodenojejunal anastomosis after extensive small bowel resection for ischaemic lesions	—	Excision of edges Sewn suture Sealed patch	Death at day 20 postoperatively Autopsy: ischaemic perforation of the jejunum Patch in place covering the suture line
Case 8 65 years	Early postoperative enterocutaneous fistula after left hemicolectomy for cancer	—	Excision of edges Sewn suture Sealed patch	Good healing (radiological evidence)

after excision of the wound edges. Details of these patients are given in *Table 1*.

In the seven patients in group 2, a patch was added to reinforce a sutured or stapled anastomosis judged to be weak because of high risk location, or septic local conditions and poor general condition. Details of these patients are given in *Table 2*.

Results

Animal studies

In the patch group, the mortality rate was zero. We observed no localized or generalized peritonitis. On day 5, the patch was well fixed on the caecum and integrated with its surroundings. The experimental wound, 7–8 mm wide, was edged by mucosal tissue. From days 5 to 20, the wound filled in gradually as the patch was progressively resorbed. By day 20, the patch had the form of a 3 mm residual granuloma while the mucosa seemed macroscopically reconstituted. The reference sutures were 1 cm away, showing that there had been no retraction (*Figure 1b*). Healing was judged completed by day 40.

Scanning electron microscope examination of samples confirmed these macroscopic findings; a crater-like depression on day 20 was completely filled with microvilli (*Figure 1c*).

Light micrographs illustrated the later healing steps. At day 20, a complete epithelium formed mainly by absorptive cells and some mucous cells was vsible but the muscle layers had not yet been restored (*Figure 1d*). On day 30, a fine muscle layer, apparently originating in the muscular mucosa, joined the two separated muscular zones (*Figure 1e*). By day 40, the two circular and longitudinal muscle layers were complete; the colonic wall was wholly reconstituted, without fibrotic reaction (*Figure 1f*). A slightly hypertrophied submucosa at this period was again normal at day 60.

In the control group, all rats died within 48 h from faecal peritonitis, except one which died at day 20 from a locoregional abscess.

Clinical evaluation

There were no postoperative complications due to the placement of an elastin patch. In group 1 patients (*Table 1*), the patched intestinal fistulae healed within 2 weeks. The control criteria were clinical (case 2), endoscopic (cases 1, 3 and 4) and radiological (cases 1, 3, 4, 5 and 8). Patients 6 and 7 died of peritonitis due to an ischaemic perforation independent of the zone patched. At autopsy, the patch was in place, and covering the suture line satisfactorily.

In group 2 patients (*Table 2*), who received reinforcing patches, there were no postoperative fistulae as judged by clinical and radiological examination. Patient number 14 (40 years) died on the 35th postoperative day from renal and respiratory insufficiency. He had had a jejunojejunal anastomosis after a perforation of the small intestine in the context of Wegener's granulomatosis. Autopsy showed that the patch was in place and adhering to the suture line it protected (*Figure 2*).

Discussion

The present study indicates that a new reconstituted connective tissue, the elastin patch, is able to assist the healing of normal

Table 2 *Details of patients in group 2*

	Diagnosis	Treatment with patch	Results
Case 9 78 years	Ischaemic perforation of the right colon with peritonitis	Extensive resection of small bowel Right hemicolectomy Stapled jejunotransverse anastomosis reinforced with a sealed patch	Good healing (clinical and radiological evidence)
Case 10 38 years	Crohn's disease Peritonitis from ileal perforation	Right ileocolectomy Stapled ileotransverse anastomosis reinforced with a sealed patch	Good healing (clinical and radiological evidence)
Case 11 50 years	Gangrenous ischaemic colitis	Left hemicolectomy Stapled low colorectal anastomosis reinforced with a sealed patch	Good healing (clinical and radiological evidence)
Case 12 71 years	Obstructing sigmoid cancer with peritonitis from perforation of the caecum	Total colectomy Ileorectal anastomosis reinforced by a sealed patch	Good healing (clinical and radiological evidence)
Case 13 65 years	Peritonitis from ischaemic perforation of the jejunum	Small bowel resection Jejunojejunal anastomosis reinforced by a sealed patch	Good healing (clinical and radiological evidence)
Case 14 40 years	Wegener's disease Peritonitis from jejunal perforation	Small bowel resection Jejunojejunal anastomosis reinforced by a sealed patch	Death on postoperative day 35 from renal and respiratory failure Autopsy: good healing of the anastomosis with patch still in place adhering to the suture (*Figure 2*)
Case 15 23 years	Double shotgun wound of the right colon	Excision of edges Suture Sealed patch	Good healing (radiological evidence)

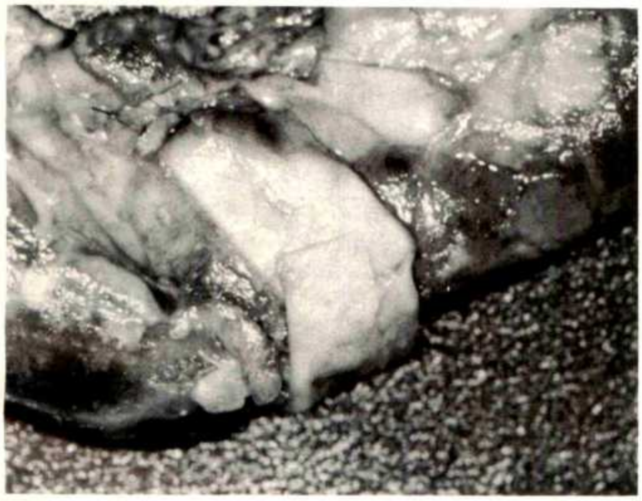

Figure 2 *Patient number 14, 35th day postoperative autopsy appearance showing absence of lysis of the patch protecting a weak jejunal anastomosis in a septic situation*

and pathological digestive tract defects. This is due to its physical and chemical properties that allow it to resist the specific constraints encountered in digestive surgery. Many investigations have been performed to improve the biochemical, structural, and physical qualities of the first product elaborated from elastin and fibrinogen, so as to improve its reliability for clinical use. Addition of type I collagen and reticulating agents such as thiourea have conferred greater cohesion. Moreover this matrix has to be protected from proteolytic enzymes, and aprotinins subserve this function.

These improved qualities of the new biomaterial are probably reflected in the results observed in unsutured wounds in the rat colon. The wound healing was rapid (20 days for the mucosa, 40 days for the muscular layers) and without inflammatory reaction. One of the interesting findings was the absence of retraction as measured by the reference sutures placed on the borders of the wound. This quality of intestinal wound healing may perhaps be related to the specific qualities of the connective tissue which must be considered not only as a mechanical patch but also as a biological extracellular matrix inducing cellular proliferation and differentiation. This type of wound healing is much superior to that obtained after omentoplasty. Omentoplasty used as a patch to cover a jejunal wound defect in the animal model led to a 66 per cent mortality rate due to peritonitis. This was related to wound leakage, and in survivors re-epithelization was slow and disorganized, with a considerable inflammatory infiltrate[3]. However, in our animal study, omental plugging or adherence seemed to give more safety to patch adhesion and to play a role in the resorption of the patch by inflammatory cells.

The successful results obtained in the animal studies with the elastin patch led us to believe that this could be an effective approach to the management and prevention of digestive fistulae in man. Indeed, anastomotic leakage is the main cause of mortality and morbidity in digestive tract surgery, in spite of improved indications, technique and perioperative care. Prevention still is a major challenge, especially in septic situations where staged surgery remains the most practical approach. A technique allowing ideal healing after intestinal anastomosis in this situation has yet to be discovered.

Biomaterials, commonly used in many surgical specialities, have not often been employed in digestive surgery because of the failure to date of the synthetic materials assessed. For example, use of wraps of polyethylene or of Silastic® (Dow Corning, Reading, UK) films around anastomoses has resulted in an increased risk of peritonitis by anastomotic leakage[4].

To date, two different technical approaches have been assessed in fistula prevention. Stapling techniques raised optimism as they reduce wound ischamia so that suture lines heal with minimal inflammation, whereas sewn suture always produce an early inflammatory reaction which leads to a weakened anastomosis[5]. Unfortunately, recent controlled studies do not demonstrate that the incidence of fistula formation has been reduced by stapling techniques[6–11], except perhaps in the case of intrathoracic oesophagogastric anatomoses[12].

Biological glue is a second preventive technique recently used in Europe. In one animal study, a fibrin glue was used without suture[13]. Usually, fibrin adhesives supplement sutured or stapled anastomoses to prevent leakage[14–16], but a reduction in leakage rate has not been convincingly shown. Tashiro *et al.*[17], using a fibrin glue in patients undergoing pancreatico-jejunostomy after pancreaticoduodenectomy, reported a statistically significant decrease in the incidence of major leaks, but the trial was not prospective. Furthermore the reasons for success were not clear for, when the fibrin glue was immersed in pancreatic juice *in vitro*, fibrinolysis occurred after 10 h, and after 15 h in the presence of aprotinin[17]. The survival time of these glues (one[13] or two[15] weeks) makes their efficacy controversial.

In our present study, the encouraging results in patients must be cautiously interpreted, as there were no controls (a prospective evaluation has yet to be conducted). However, the healing of eight major fistulae in group 1 is notable (especially cases 1, 3 and 4 in which the original surgeon had undertaken one or two conventional reinterventional operations). In group 2, evaluation is more difficult but, if the patches cured the fistulae of group 1 patients, they hopefully can prevent leakage from a high risk sutured anastomosis. Case 10, that of a young patient operated upon for peritonitis following ileal perforation in Crohn's disease is particularly significant in that patch placement required a single operation without stoma creation, whereas the classical approach would have forbidden anastomosis and led to a staged operation.

Opinions concerning the widespread use of the elastin patch and sealant in practice may be reserved, since commercial fibrinogen concentrate prepared from pooled donors is not universally accepted because of the risk of the transmission of viral infection, particularly hepatitis B and the human immunodeficiency virus (HIV). In fact, the human elastin for the patch is extracted in 1 M NaOH for 1 h at 90°C, conditions sufficient to destroy any virus. For the sealant and the cold insoluble proteins, the human donors are limited to 30, all of whom must be hepatitis B virus and HIV antigen negative. A procedure for viral inactivation of the sealant is now being officially evaluated. Furthermore several procedures may now be used to avoid using pooled donors to obtain the fibrinogen concentrate; these include the preparation of fibrin glue from single-donor fresh frozen plasma[18], or from the patient's own blood[19,20].

In conclusion, the elastin patch technique offers the prospect of reducing the occurrence of digestive tract fistulas. Because it is the first biomaterial of its kind to be used for this indication, it allows comparison with other biomaterials being considered for the same indication. This biomaterial has to be considered as a prototype. Certainly more adaptable and resistant biomaterials will be developed in the future. If it is shown by a prospective study that such biomaterials effectively prevent leakage from high risk anastomoses, it is possible that certain multistage surgical procedures would be rendered obsolete, and that there would be less use of or perhaps complete avoidance of protective stomas.

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Comparison between anal endosonography and digital examination in the evaluation of anal fistulae

A prospective trial was performed comparing the accuracy of digital examination and anal endosonography in defining the anatomy of anal fistulae. Before operation 38 consecutive patients were assessed by the consultant in charge of the case, by a research fellow and by anal endosonography involving two radiologists. These findings were compared with the operative findings. Consultants correctly identified 26 of 33 internal openings, 29 of 34 primary tracks and 15 of 21 secondary tracks. The research fellow correctly identified 26 internal openings, 24 primary tracks and 10 secondary tracks. There was no significant difference between the accuracy of consultants and the research fellow. Anal endosonography identified 10 internal openings based on initial criteria. This rose to 24 when revised ultrasonographic criteria were applied. There was no statistical difference between consultant assessment and anal ultrasonography in correctly identifying intersphincteric and transphincteric tracks. Ultrasonography is unable to assess primary superficial, suprasphincteric and extrasphincteric tracks or secondary supralevator and infralevator tracks. Consultant assessment of secondary supralevator and infralevator tracks was correct in 78 per cent of cases.

S. Choen, S. Burnett*, C. I. Bartram* and R. J. Nicholls

Departments of Surgery and
**Radiology, St. Mark's Hospital,*
City Road, London EC1V 2PS, UK
Correspondence to:
Mr R. J. Nicholls

A large proportion of fistulae *in ano* are simple to manage surgically[1]. Complex fistulae, however, are more likely to be followed by postoperative recurrence and incontinence[2]. An accurate delineation of their anatomy before operation is therefore important. Fistulography has been shown to have little place in routine management[3]. Initial experience with anal endosonography has suggested that it may have a role in the assessment of the complex fistula[4], although its accuracy in relation to digital examination has not been assessed. This prospective study was undertaken to compare the accuracy of digital assessment with anal endosonography.

Patients and methods

Thirty-eight consecutive patients admitted to one hospital between 1 September 1989 and 31 December 1989 were studied prospectively before surgery for anal fistulae or perianal sepsis.

Anal endosonography

Anal endosonography was performed on the day before surgery by one of the radiologists using a previously described technique[4]. The patient was examined in the left lateral position using a Bruel and Kjaer (Naerum, Denmark) ultrasound scanner. This has a 7 MHz rotating endoprobe of 3 cm focal length, fitted with a special hard sonolucent cone, containing degassed water, of 1·7 cm external diameter for maintaining acoustic coupling. The probe was introduced into the anal canal and serial images taken during its withdrawal.

Early review of the data showed that the ultrasonographic criteria previously described[4] for the identification of internal openings were inadequate. A break in the mucosal layer which was the chief criterion previously used was found to correlate poorly with the site of an internal opening. This sign was therefore excluded from the ultrasonographic criteria for identifying an internal opening, which thereafter included one or more of the following features: a hypoechoic breach of the subepithelial layer of the anorectum, a defect in the circular muscles of the internal anal sphincter, and a hypoechoic lesion of the normally hyperechoic longitudinal smooth muscle abutting on the normally hypoechoic circular smooth muscle.

Primary tracks were identified by the following features. An intersphincteric track was seen as a hypoechoic line running through the normally hyperechoic longitudinal smooth muscle. A transphincteric extension was indicated by a hypoechoic line extending outwards through the external anal sphincter. Using the present endoanal ultrasound equipment, it was not possible technically to assess supralevator, infralevator, extrasphincteric, suprasphincteric or superficial tracks. The ultrasonographic films were assessed using these criteria blind by the consultant radiologist who reviewed the entire series of 38 patients on completion of the clinical part of the study.

Digital assessment

Digital examination was carried out before operation under anaesthesia with the patient in the lithotomy position. It was first performed by the research fellow of senior registar grade and then by the consultant in charge of the case. Probes were not used during these digital examinations in accordance with the usual assessment of fistula *in ano* at this hospital.

Data analysis

All ultrasonography and digital examinations were performed blind. Assessments were recorded on data sheets (*Figure 1*) and the operative delineation of the anatomy of the fistula was the final arbiter of accuracy. The accuracy of the clinical and ultrasound assessments were compared using the χ^2 test with Yates' correction and Fisher's exact test.

Results

Before operation anal endosonography was performed in 36 of the 38 patients; it was not carried out in two because of severe pain. Surgical exploration revealed 33 internal openings. Four superficial abscesses and one intersphincteric sinus did not have an apparent internal opening. A primary track was found in 34 cases and 21 patients had a secondary track. The consultants correctly identified the location of 26 of 33 internal openings, 29 of 34 primary tracks and 15 of 21 secondary tracks. The research fellow correctly identified 26 internal openings, 24 primary tracks and 10 secondary tracks. Of the 34 primary

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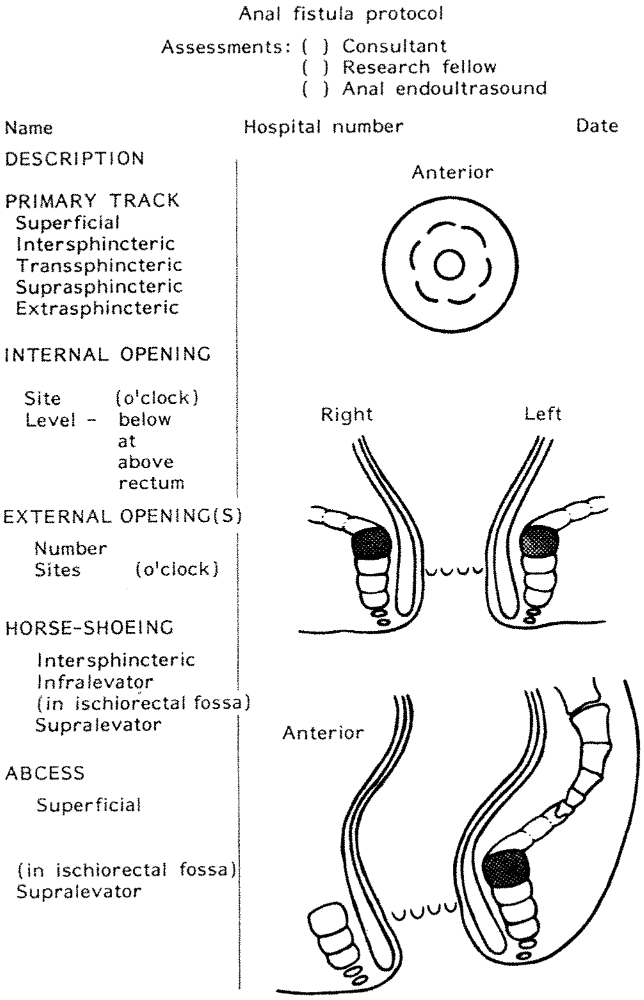

Anal fistula protocol

Assessments: ( ) Consultant
( ) Research fellow
( ) Anal endoultrasound

Name Hospital number Date

DESCRIPTION

PRIMARY TRACK
Superficial
Intersphincteric
Transsphincteric
Suprasphincteric
Extrasphincteric

INTERNAL OPENING

Site (o'clock)
Level - below
at
above
rectum

EXTERNAL OPENING(S)

Number
Sites (o'clock)

HORSE-SHOEING

Intersphincteric
Infralevator
(in ischiorectal fossa)
Supralevator

ABCESS

Superficial

(in ischiorectal fossa)
Supralevator

Figure 1 *Data sheet design used for assessment of fistula* in ano

tracks, 12 were intersphincteric, 14 were transphincteric, four were extrasphincteric and four were superficial. Consultants correctly assessed 10 of 12 intersphincteric, 14 of 14 transphincteric, 1 of 4 extrasphincteric and 4 of 4 superficial tracks. The research fellow correctly assessed 10 of 12 intersphincteric, 10 of 14 transphincteric, 0 of 4 extrasphincteric and 4 of 4 superficial tracks. There were no suprasphincteric primary tracks in this series. Of the 21 secondary tracks, three were intersphincteric, 11 were supralevator and seven infralevator. Consultant assessment was correct in 1 of 3 intersphincteric, 7 of 11 supralevator and 7 of 7 infralevator cases and the research fellow in 0 of 3 intersphincteric, 6 of 11 supralevator and 4 of 7 infralevator cases. There was no statistical difference between the accuracy of consultants and the research fellow in any of these assessments (*Tables 1, 2* and *3*).

Anal endosonography identified ten internal openings using the initial criteria[4]; this rose to 24 when the revised criteria were applied. It correctly identified 10 of 15 intersphincteric tracks and 11 of 14 transphincteric tracks (primary and secondary tracks included). There was no statistical difference between consultant assessment and anal endosonography in the assessment of internal openings, intersphincteric or transphincteric tracks (*Table 4*).

Discussion

This study is the first prospective study assessing clinical accuracy in anal fistulae. The findings at operation, taken as the standard against which the preoperative clinical and endosonic assessments were compared, cannot be regarded as being absolutely correct. The failure to find an internal opening in five of the 38 cases indicates that this may be so. However, they were the best available means of identifying the surgical anatomy. Those doing the operations were experienced in this type of surgery and the location of the internal openings found, the classification of primary tracks and the presence and sites of any secondary tracks and abscesses were clearly evident on surgical exploration. Consultant colorectal surgeons were able to make accurate digital assessments of the anatomy of anal fistulae in the majority of cases. The research fellow was also able to accumulate skill and experience in a relatively short time of apprenticeship with the consultants. The proctologist should aim to assess the anatomy of anal fistulae accurately.

Table 1 *Comparison of the accuracy of digital examination and anal ultrasound in the assessment of internal openings of anal fistulae*

Position of internal opening	Operative finding	Consultants	Research fellow	Ultrasonography criteria Old	Ultrasonography criteria New
Anterior	7	5	5	1	4
Posterior	22	20	19	9	18
Lateral	4	1	2	0	2
Total	33	26	26	10	24

Table 2 *Accuracy of digital assessment of primary tracks of anal fistulae*

Primary tracks	Operative finding	Consultants	Research fellow
Intersphincteric	12	10	10
Transphincteric	14	14	10
Suprasphincteric	0	0	0
Extrasphincteric	4	1	0
Superficial	4	4	4
Total	34	29	24

There was no significant difference in accuracy between consultants and research fellow

Table 3 *Accuracy of digital examination in defining the secondary tracks of anal fistulae*

Secondary tracks	Operative finding	Consultants	Research fellow
Supralevator	11	7	6
Infralevator	7	7	4
Intersphincteric	3	1	0
Total	21	15	10

There was no significant difference in accuracy between consultants and research fellow

Table 4 *Comparison of digital examination and anal endosonography in anal fistulae*

Track	Surgical finding	Consultant	Ultrasound
Intersphincteric	15	11	10*
Transphincteric	14	14	11*
Suprasphincteric	0	0	NA
Extrasphincteric	4	1	NA
Superficial	4	4	NA
Supralevator	11	7	NA
Infralevator	7	7	NA
Total	55	44	21

*There was no significant difference between consultant and ultrasound. NA, not possible to assess

Digital anorectal examination should not be superseded by technology without good reason.

There are several important pointers for an accurate anorectal examination in anal fistulae. Careful inspection of the perineum is important. Intersphincteric tracks usually open externally very close to the anal verge, although they may sometimes track subcutaneously for a longer distance before discharging. Transphincteric and other more complicated tracks by definition will open further away as they will have to traverse the external anal sphincter first. The clockface position of the internal opening will have been suspected by Goodsall's rule as well as by the radial direction of the track on perianal palpation. The internal opening is felt as an indurated nodule or by a pit in the epithelium of the anorectum. Fistula tracks are felt on rectal examination as induration and often asymmetry between the right and left sides. Bidigital examination will define the relationship of the track to the anal sphincters and also gives a good indication of anal sphincter bulk. With careful examination, an accurate evaluation of the anatomy of anal fistulae can be made in most cases. Fistula probes were not used in this study.

Anal endosonography correctly identified the internal openings of many of the cases examined. The initial endosonographic sign of a break in the mucosal layer used for the identification of internal openings[4] missed a significant number of internal openings. Internal openings had been said to be difficult to detect as they did not lie within the focal range of the anal probe[4]. The present study has shown that with the exclusion of this feature from the criteria for the identification of internal openings, the accuracy of anal endosonography has increased. The technique is also capable of correctly detecting a large proportion of intersphincteric and transphincteric tracks. We have no experience of the use of hydrogen peroxide to show up tracks and openings during ultrasound examination. At present ultrasonography cannot detect primary superficial, extrasphincteric and suprasphincteric tracks or secondary supralevator and infralevator tracks. There are two main reasons for this. First, the special hard sonolucent cone used to image the anal canal[4] will not make contact with the rectum, so losing acoustic coupling with the rectal mucosa. An examination of the rectum with the standard endorectal balloon (to maintain acoustic coupling above the level of the levator ani), immediately after anal endosonography might perhaps improve the accuracy for supralevator lesions. Second, the focal length of the endoanal probe is 3 cm, giving insufficient penetration of the ultrasonic beam beyond the external anal sphincter. Supralevator and infralevator extensions including ischiorectal tracks are therefore not imaged clearly with the present equipment. Perhaps this will be possible with the development of longer focal length probes. Correct assessment of secondary tracks within the supralevator and ischiorectal regions is, however, important as these must be correctly identified to be adequately drained or laid open. In this regard, clinical examination had the clear advantage.

Anal endosonography is also difficult in patients with previous anal sepsis, surgery or trauma, as residual scars or defects will confuse ultrasonographic interpretation and differentiation from anal fistulae. Care must also be taken not to confuse intersphincteric tracks with smooth muscle bands that may run concentrically within the longitudinal smooth muscle layer.

Anal endosonography is in the development phase but may still be helpful when clinical examination is confusing or uncertain. Further study of this particular aspect is in progress.

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Confirmation of endosonographic detection of external anal sphincter defects by simultaneous electromyographic mapping

S. J. D. Burnett, C. T. M. Speakman*, M. A. Kamm* and C. I. Bartram

Departments of Radiology and Physiology, St. Mark's Hospital, London EC1V 2PS, UK*

Correspondence to:
Dr C. I. Bartram

Anal endosonography was performed in 13 consecutive patients with post-traumatic faecal incontinence. Thirteen acoustic defects in the external anal sphincter (two hyperechoic, four of mixed echogenicity and seven hypoechoic) were analysed electromyographically by locating under ultrasound guidance the tip of a concentric needle within the defect. The electromyographic activity in this zone was compared with ultrasonically normal muscle. Eleven of 13 sonographic defects showed no electrical activity on electromyography, there was one technical electromyography failure, and one defect was too deep to be reached by the electromyography needle. The electromyographic response was normal in each case within ultrasonically normal muscle. Anal endosonography is recommended as the initial investigation to locate defects, which may be confirmed electromyographically thereby limiting the number of painful needle insertions required for complete mapping of the external anal sphincter.

The technique of electromyography using concentric needle electrodes is an established part of the physiological investigation of pelvic floor disorders[1,2] to assess the electrical activity of striated muscle[3,4]. The electromyographic activity is reduced where the number of functioning fibres is reduced. Needle insertions into the four quadrants around the anus allows an approximate mapping of the external anal sphincter to determine areas of residual muscle following sphincter division[5]. A detailed evaluation to plan remedial surgery[6,7] involves many more needle insertions. This is particularly painful anteriorly in women, and even in normal subjects the anterior part of the external anal sphincter is thin[1], making assessment of this part of the external anal sphincter difficult.

Recently anal endosonography has been used to image the sphincter muscles[8] and assess their integrity[9]. Histological confirmation that acoustic defects in the external anal sphincter actually represent areas of muscle deficiency with fibrosis has not proved possible, as collecting tissue samples during surgery is difficult. The validity of sonographic mapping has been based on comparative studies between electromyography and anal endosonography, which have shown good correlation between acoustic and electrical 'defects' in the external anal sphincter[9]. There has been no exact demonstration of the electrical activity in areas where the external anal sphincter appears abnormal ultrasonically, in comparison with apparently normal areas of muscle.

Percutaneous needle insertion under ultrasound guidance has been a standard practice for almost two decades[10] and allows exact anatomical location of the needle tip. By inserting the concentric electromyography needle under ultrasound guidance into areas of sonographic 'defects' and apparently normal muscle it has been possible to relate the sonographic findings directly to the electromyographic activity.

Patients and methods

Thirteen consecutive patients (four men, nine women) with incontinence to solid faeces secondary to trauma were investigated. In eight patients incontinence had developed following obstetric trauma, two after anal surgery and three following road traffic accidents. Electromyography and anal endosonography were performed as part of the routine assessment.

Anal endosonography was undertaken 'blind' before electromyography with the radiologist unaware as to the site of any possible defect. A Brüel and Kjær (Harrow, UK) 7 MHz rotating transducer of 3 cm focal length was used, covered with a hard sonolucent plastic cone of 1·7 cm external diameter, and filled with degassed water for acoustic coupling. The assembled unit was lubricated, inserted with the patient in the left lateral position and serial images taken.

Once a defect had been identified the concentric electromyography needle tip was positioned within the sonographic defect under ultrasound guidance. Recordings were taken from this site and the needle then reinserted in an area of sonographically normal external anal sphincter, again with ultrasound localization. Electrical activity was noted at rest and with the patient straining. During electromyography recording the ultrasound transducer was switched off to reduce artefact. The arc over which the defect extended was measured and described in terms of the hours on a clock face – 12 o'clock being anterior.

Results

Thirteen defects were found by anal endosonography in 12 of the 13 patients. Of these defects, two were hyperechoic, four were of mixed echogenicity and seven were hypoechoic. One patient had no detectable defect, subsequently confirmed by electromyography mapping.

Eleven of the 13 acoustic defects electromyographically showed no electrical activity (*Figures 1* and *2*). Of the remaining two defects, a technical failure of the electromyography equipment in one patient prevented confirmation, and in the other the defect was too deep to be reached by the electromyography needle. The needle tip was clearly visualized within the defect in every other case. Normal electromyographical responses were found within muscle considered to be sonographically normal in each case (*Figures 3* and *4*). These results are summarized in *Table 1*.

In addition the anal endosonography revealed defects in the internal anal sphincter in nine of the 13 patients.

Discussion

Anal endosonography is currently the only method available for obtaining detailed images of the internal and external anal sphincters. The normal anatomy is shown in *Figure 5*. With

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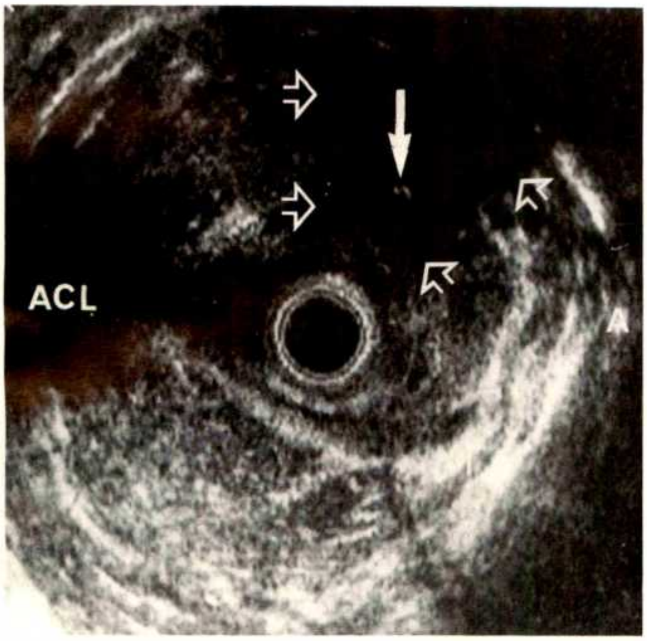

Figure 1 *Electromyography needle tip localized (closed arrow) within the hypoechoic external sphincter defect (open arrows). The patient is examined on the left side, and the probe rotated so that the image is in a comparable position with anterior (A) on the right side. This image is taken in the mid level of the external sphincter, and the posteriorly placed anococcygeal ligament (ACL) is seen on the left side of the picture*

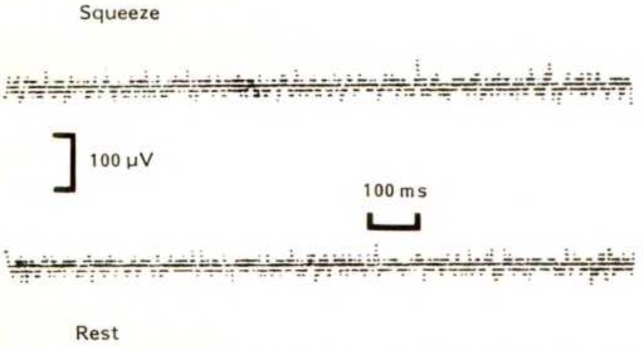

Figure 2 *Electromyography tracing from the needle in* Figure 1, *showing no increased electrical activity during squeeze from the defect*

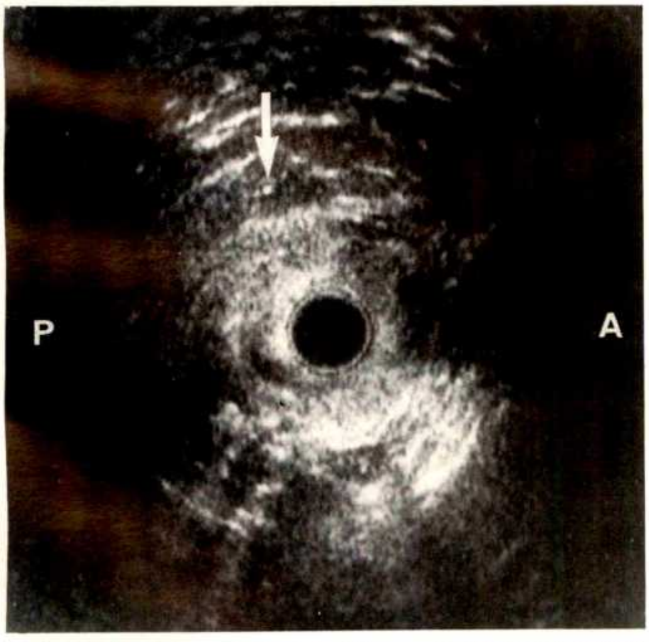

Figure 3 *Needle (arrow) situated within acoustically normal external anal sphincter. A, anterior; P, posterior*

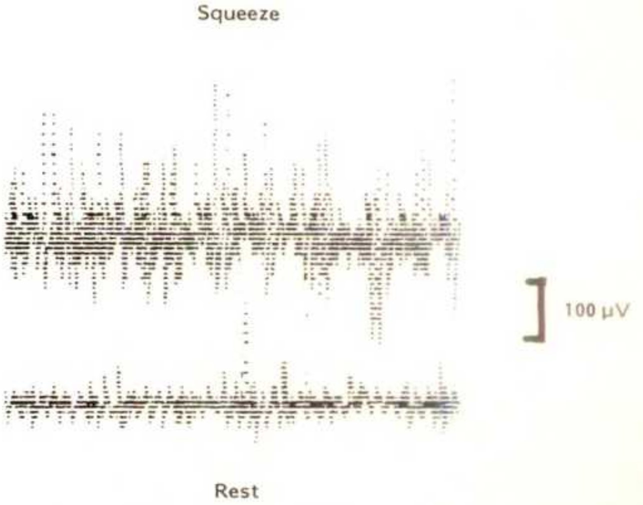

Figure 4 *Electromyography tracing from the needle in* Figure 3, *showing a normal increase in electrical activity during squeeze*

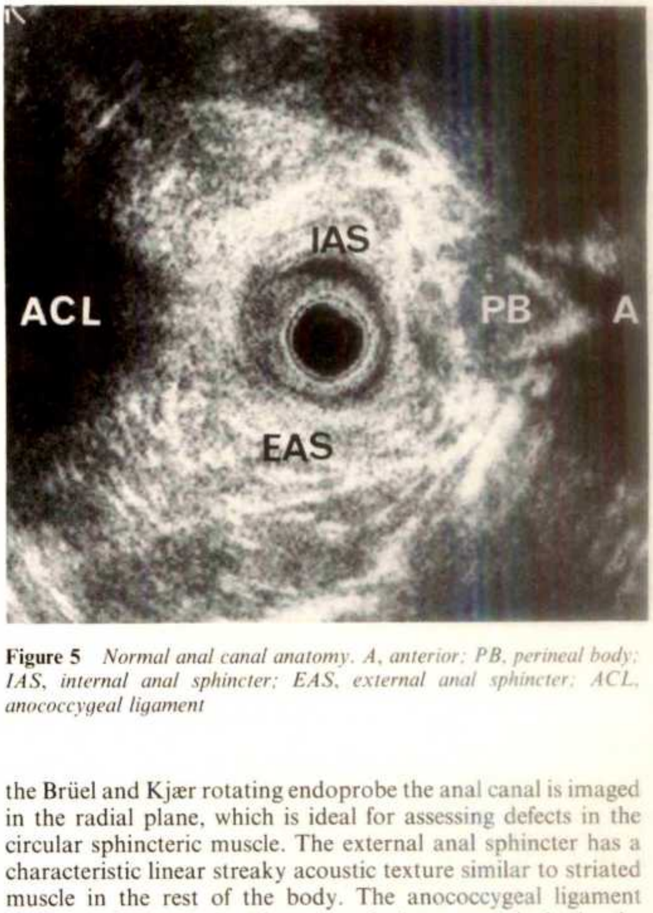

Figure 5 *Normal anal canal anatomy. A, anterior; PB, perineal body; IAS, internal anal sphincter; EAS, external anal sphincter; ACL, anococcygeal ligament*

the Brüel and Kjær rotating endoprobe the anal canal is imaged in the radial plane, which is ideal for assessing defects in the circular sphincteric muscle. The external anal sphincter has a characteristic linear streaky acoustic texture similar to striated muscle in the rest of the body. The anococcygeal ligament creates a hypoechoic triangular shadow posteriorly in the superficial part of the external anal sphincter, which should not be confused with a defect. The anatomy of the external anal sphincter anteriorly is complex and variable. The deep and superficial parts of the external anal sphincter are much thinner anteriorly than posterolaterally and their fibromuscular insertions fuse in the perineal body whch is larger in women. The subcutaneous part of the external anal sphincter has no bone attachment and circular muscle fibres should be visible anteriorly.

The post-traumatic defects in the external anal sphincter showed a variable acoustic appearance, for reasons as yet undetermined. The diagnostic features common to all the defects were discontinuity of the normal muscle pattern with a homogeneous area of predominantly either hyperechoic, hypoechoic, or mixed echogenicity merging on either side into

Table 1 *Ultrasound and physiology results*

Age (years)	Sex	Aetiology	Resting pressure (cmH_2O)	Squeeze pressure (cmH_2O)	Pudendal neuropathy	Site (in hours)	Size (in hours)	Echogenicity	Internal anal sphincter defect
63	M	Surgery	45	40	No	4–6	2	Increased	Yes
50	F	Obstetric	80	15	Yes	9–11	2	Increased	Yes
55	M	RTA	20	10	Yes	5–1	8	Decreased	Yes
						12–1	2	Decreased	
54	F	Obstetric	25	20	Yes	10–11·30	1·5	Decreased	No
40	M	RTA	15	40	No	4–8	4	Decreased	Yes
28	F	Obstetric	75	5	Yes	11–1	2	Mixed	Yes
39	F	Obstetric	50	60	Yes	10·30–1	2·5	Decreased	Yes
39	M	Surgery	60	120	No	–	–	–	Yes
60	F	Obstetric	50	20	Yes	9–11	2	Mixed	No
36	F	Obstetric	80	30	Yes	9–11	2	Decreased	No
30	F	Obstetric	70	40	No	10–1	3	Mixed	Yes
30	F	RTA	20	40	Yes	6–1	7	Decreased	Yes
34	F	Obstetric	–	–	–	9–12	3	Mixed	No

RTA, road traffic accident

normal muscle. There was no relation between the echogenicity of the defect and its aetiology. One patient has had surgery so far and no macroscopic correlation is available. Every acoustic defect was shown to be devoid of electrical activity irrespective of its echo pattern.

The anal canal radiologically averages 4 cm in length[11]. Allowing for skin thickness it is to be expected that the deep aspects of the external anal sphincter would be beyond the reach of the standard 3 cm concentric needle. An advantage of anal endosonography is that defects can be mapped in their depth and radial extent. With routine electromyography needle insertions of 1–2 cm, only the superficial parts of the sphincter will be examined and a deep lesion either missed altogether or the true extent of depth of the defect not appreciated.

The smooth muscle of the internal anal sphincter is precisely defined during the investigation. Faecal incontinence may be due to damage to the internal sphincter and information about the integrity of this part of the sphincter complex is valuable. Eight of the patients were shown to have a defect in the internal sphincter, including one whose external sphincter was intact. These did not appear to be more common in any one type of trauma.

Anal endosonography and electromyography are technically difficult investigations. Anal endosonography demonstrates defects in the internal sphincter but the interpretation of lesions in the external anal sphincter is more complex and requires electromyographic confirmation before surgical repair. Anal endosonography is unable to detect denervation of the external anal sphincter but it is a pain-free and relatively rapid examination suitable for screening. It is recommended that anal endosonography is performed first to detect any external anal sphincter defect and record its radial and linear extent. This will provide a target area for confirmation by electromyography and reduce the number of needle insertions required for detailed mapping of the external sphincter.

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Role of a regional register for familial adenomatous polyposis: experience in the Northern Region

Within 36 months of its formation the Northern Region Polyposis Registry had increased the number of identified gene carriers of familial adenomatous polyposis from 56 to 65 in a population of 3·1 million and had achieved a 15-fold increase in the number of at-risk relatives being regularly screened. Review of the surgical records at the outset of the registry revealed that the mean age at diagnosis of those patients detected by screening was 24·7 years, whereas it was 36·6 years for those detected by symptoms. Ten of the 31 in the latter group had colorectal carcinomas whilst only one of those detected by screening had a cancer and a significantly higher proportion had sphincter-saving surgery. A regional registry can provide an effective screening and counselling service to surgeons treating patients with familial adenomatous polyposis. At-risk relatives are best assessed by combining results of the different screening procedures now available but the prime requirement of a successful registry is dedicated domiciliary counselling.

**M. Rhodes*,
P. D. Chapman†, J. Burn†
and A. Gunn**

Department of Surgery, Ashington General Hospital, Northumberland NE63 0SA and †Regional Genetics Advisory Service, Newcastle upon Tyne NE2 4AA, UK

Correspondence to:
Mr A. Gunn

The possibility that colorectal adenomas could be familial was first recognized by Cripps in 1882[1] who described two siblings with multiple colorectal adenomas. In 1925 Lockhart-Mummery drew attention to the risk of malignant transformation of familial large bowel adenomas[2]. The subsequent formation of the St. Mark's Polyposis Registry and the writings of Dukes[3] have further clarified the nature of familial adenomatous polyposis (FAP) and demonstrated the need for prophylactic surgery. A large literature has accumulated and several registers have been developed in different parts of the world[4–6] but as yet there are no comprehensive registers of defined geographical areas in the UK. In 1987 a regional register was established within the Northern Region of England so that surgeons could have a genetic service available to help them trace and screen at-risk relatives of patients with FAP and assess the need for surgical intervention. The results of the first 36 months of this register are presented with an emphasis on the implications for surgical management.

Patients and methods

All 72 general surgeons employed within the Northern Regional Health Authority of England (population 3·1 million) agreed to provide details of patients under their care with FAP. A part-time genetic nurse (P.D.C.) worked with a consultant clinical geneticist (J.B.) and a consultant surgeon (A.G.) to carry out a systematic search for affected families with the assistance of the surgical units involved. All families were visited, pedigrees constructed and arrangements made to compile a dedicated microcomputer register to provide a recall service for screening. Verbal permission was obtained from all patients and relatives interviewed for their inclusion in the register, and more recently written consent has been requested. The requirements of the Data Protection Act (1984) have been observed during computerization of records.

Family members were recommended to attend for screening by the surgeon responsible for their affected relative, although some flexibility was necessary in relation to the place of residence and in the situation where more than one surgeon was responsible for different branches of the same family.

During the course of the first year it became apparent that multiple areas of congenital hypertrophy of the retinal pigment epithelium, detected by indirect fundoscopy (*Figure 1*), was a useful sign enabling identification of carriers of the gene[7,8]. Subsequently all obligate gene carriers and patients at risk were seen in an ophthalmological research clinic to assess this particular clinical feature. Blood samples were obtained from all family members to assess the reliability of available gene markers. Detailed results of this aspect of the Registry's work will be reported at a later date[9]. The notes of all living affected obligate gene carriers were reviewed in order to validate pathological reports and obtain details of surgical techniques employed.

Results

Table 1 illustrates the management of FAP in the Northern Regional Health Authority of England as assessed by a review of the case records of all living patients treated at January 1987.

Between January 1987 and January 1990 the number of patients detected with FAP rose from 56 to 65. Over the same period the number of at-risk relatives under review rose from 21 to 308.

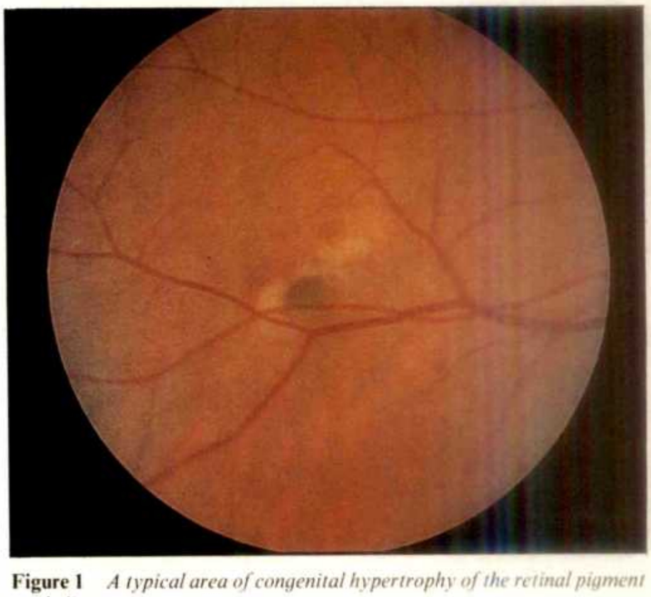

Figure 1 *A typical area of congenital hypertrophy of the retinal pigment epithelium*

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* *Current address: Department of Surgery, Royal Victoria Infirmary, Newcastle upon Tyne, UK*

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Table 1 *Management of familial adenomatous polyposis in the Northern Region at January 1987*

	Detected by screening	Detected by symptoms
No. of patients	25	31
Mean age at diagnosis (years)	24·7	36·6
Surgery performed		
Colorectomy and ileorectal anastomosis	9	11
Proctocolectomy and ileal reservoir	6	1
Panproctocolectomy	5	13
Patients with colorectal carcinoma at the time of surgery	1	10

Discussion

During the first 36 months of its existence, the Northern Regional Polyposis Registry identified nine new gene carriers with FAP, a 16 per cent increase in the total of 56 identified at the initial review. The 15-fold increase in the number of relatives screened should prove important, as active identification of potential gene carriers should, in the long term, lead to early operative intervention and a subsequent reduction in morbidity and mortality rates. This belief is supported by the observation that ten of the 31 patients who were referred for surgery on the basis of symptoms (average age 36·6 years) had a colorectal carcinoma whereas only one of the 25 detected by screening (average age 24·7 years) was so affected. This, together with the lower incidence of panproctocolectomy in the population detected by screening, is encouraging, although patients undergoing rectal sparing surgery remain at risk of developing cancer of the rectal stump. However, in patients who have undergone colectomy and ileorectal anastomosis for FAP the risk of death from cancer of the rectal stump is relatively small; they are more likely to die from other diseases, particularly carcinoma of the upper gastrointestinal tract[10–12].

A regional registry responsible for tracing relatives of affected patients should also be able to advise on the use and interpretation of available screening techniques. Although large bowel endoscopy remains a fundamental screening requirement, the significance of this examination is increased if the results are correlated with age. For example, it can be estimated that a 15-year-old first-degree relative with a negative sigmoidoscopy has a 30 per cent chance of carrying the affected gene, but a 30-year-old first-degree relative without detectable colorectal adenomas has a less than 1 in 10 chance of being affected[13]. In addition, the recent localization of the FAP gene to the long arm of chromosome 5 means that analysis of blood samples by DNA probes will become an increasingly important screening procedure[14]. A simple means of identifying at least 80 per cent of gene carriers is the detection of multiple areas of congenital hypertrophy of the retinal pigment epithelium by indirect fundoscopy (*Figure 1*)[7,8]. These results can be combined by standard genetic risk calculations using Bayes' theorem to give a more precise estimate of the risk of carrier status[15]; for example, a 30-year-old first-degree relative with negative bowel and eye examinations and a favourable DNA pattern has less than a 1 in 1000 chance of being a gene carrier[16]. Family members identified as being at very low risk of carrying the gene can be offered a reduced frequency or discontinuation of large bowel endoscopy. Conversely, those shown to be at high risk can be targeted more efficiently.

The combination of a consultant surgeon with an interest in colorectal disease and a consultant clinical geneticist working with a genetic nurse has proved effective. Involvement with genetics is crucial and eminently feasible now that the UK has an established specialty of Clinical Genetics with NHS consultant provision in all regions. Important too are genetic nurses equipped to visit families in their homes and, where necessary, to collect blood samples. As screening methods become more sophisticated the main requirement of an effective registry is the ability to trace and counsel at-risk individuals.

At its initiation the Northern Regional Registry relied on the St. Mark's Polyposis Registry for guidance on screening policy and recommended surgical procedures. A logical and desirable development would be the establishment in each region of the UK of a polyposis registry with connections with St. Mark's registry to permit collation of results and to allow dissemination of the rapidly growing knowledge of the most effective approaches to screening. If registries are to collate data it will be necessary to obtain consent from patients and relatives specifically for this purpose.

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Endoscopic balloon dilatation as a therapeutic option in the management of intestinal strictures resulting from Crohn's disease

A. J. K. Williams and K. R. Palmer

Gastro-Intestinal Unit, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK

Correspondence to:
Dr K. R. Palmer

Endoscopic balloon dilatation was undertaken in seven patients who presented with obstructive symptoms resulting from Crohn's disease. Five patients had strictures from recurrent disease at the site of an ileotransverse anastomosis, one had duodenal stenosis and one a colonic stricture. The procedures were performed under intravenous sedation on one to four occasions (median 2) and were uncomplicated. Sustained improvement over an 18–24-month follow-up period was achieved in five patients, but dilatation was unsuccessful in two cases. Endoscopic balloon dilatation is a safe and effective option in selected patients with intestinal strictures resulting from Crohn's disease and may overcome the need for surgery.

The majority of patients who develop Crohn's disease undergo abdominal surgery and, because recurrence is common, many will undergo multiple operations[1,2]. The realization that surgery is not curative and the need to conserve functional intestine have resulted in the concept of a conservative surgical approach to Crohn's disease[3,4]. This is exemplified by limited intestinal resection and the use of stricturoplasty. These operations are usually performed following failed medical treatment when the intestinal lumen is irreversibly narrowed by fibrosis resulting from the inflammatory process.

Fibrous strictures elsewhere in the gastrointestinal tract may be amenable to treatment by endoscopic balloon dilatation which is routinely and successfully used in the treatment of peptic oesophageal strictures[5] and pyloric stenosis[6]. This technique might be extended to fibrous strictures resulting from Crohn's disease, perhaps overcoming the need for surgical resection or stricturoplasty, or at least allowing delay of an operation while awaiting a general improvement in the patient's condition. This is a report of a preliminary experience of endoscopic balloon dilatation for Crohn's strictures.

Patients and methods

Endoscopic balloon dilatation was used in the treatment of Crohn's strictures in four men and three women between January 1987 and January 1989. Crohn's disease was diagnosed clinically and radiologically and was confirmed histologically in each case.

Five patients underwent dilatation because of recurrent attacks of small bowel obstruction from recurrent Crohn's disease at the site of a previous ileotransverse anastomosis (*Figure 1*). One patient presented with chronic gastric outflow obstruction and malnutrition caused by duodenal involvement, having had two previous ileal resections for Crohn's disease. The final patient presented with recurrent subacute large bowel obstruction from an isolated stricture in the descending colon, although she also had evidence of inactive ileal Crohn's disease. All patients had previously been treated medically, with corticosteroids (all cases), sulphasalazine (four cases), azathioprine (two cases) and/or an elemental diet (three cases), but had failed to achieve sustained remission of their symptoms. All patients had intestinal strictures <4 cm in length, accessible to the colonoscope or gastroscope. Although the Crohn's disease activity index was not formally measured, all patients were deemed to have inactive disease at the time of endoscopy and none had elevation of C-reactive protein, erythrocyte sedimentation rate or platelet count.

Balloon dilatation was performed using the commercially available 'Rigiflex' balloon system (Keymed Ltd., Southend, UK). Balloons 18 and 20 mm in diameter were used. Patients with ileocolonic or colonic strictures underwent standard colonoscopic bowel preparation using Pilocax® (Ferring Pharmaceuticals Ltd., Feltham, UK). Following intravenous sedation with midazolam (Hypnoval®, Roche Ltd., Welwyn Garden City, UK) and pethidine, colonoscopy was performed using an Olympus IT10L (Olympus-Keymed, Southend, UK) colonoscope. The stricture was identified and biopsied and the balloon inserted through the stricture. The balloon was then partially inflated and withdrawn to an optimum position before inflation to its maxium diameter for a period of 1 min. It was deflated and then reinflated for a further 2 min. Radiological screening was not performed routinely. The patient with the duodenal stricture was sedated with midazolam and pethidine and gastroscoped using an Olympus IT10 forward viewing gastroscope. Dilatation was then performed exactly as described for the colonic and ileocolonic strictures. Following endoscopy, patients were fasted for 4 h and observed in hospital for a 24-h period. In two cases the endoscopist felt that the dilatation had been incomplete because he was unable to pass the endoscope into proximal bowel following dilatation. In these instances repeat dilatation was performed. In other cases endoscopic dilatation was repeated following symptom recurrence (*Table 1*).

Response to therapy was judged on the basis of symptomatic improvement. The median length of follow-up was 24 months (range 21–27 months).

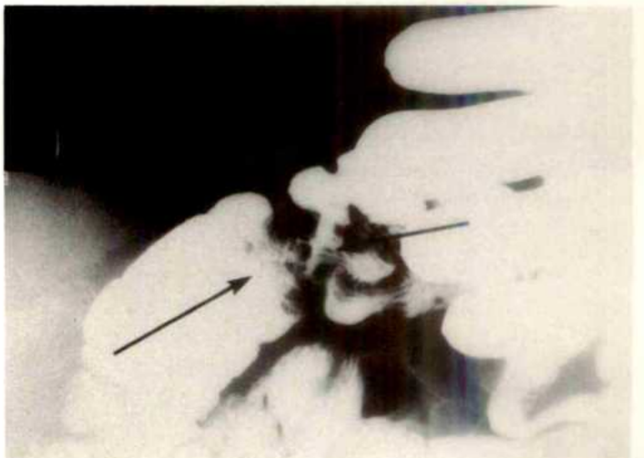

Figure 1 *Contrast study of ileotransverse anastomotic recurrence of Crohn's disease in patient 1 of* Table 1

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Table 1 *Results of endoscopic balloon dilatation*

Patient	Site of stricture	No. of dilatations	Symptoms before dilatation	Symptomatic outcome
1	Ileotransverse anastomosis	2	Subacute small bowel obstruction occurring every 4–8 weeks	Asymptomatic
2	Ileotransverse anastomosis	3	Four attacks of small bowel obstruction over previous 6 months	Technical failure
3	Duodenum	4	Gastric outflow obstruction, weight loss, serum albumin 30 g/l	Weight gain, normal serum albumin, some sensation of abdominal 'fullness' only
4	Ileotransverse anastomosis	1	Two attacks of small bowel obstruction	Episodic mild pain and distension
5	Colonic	2	Episodic abdominal distension, constipation and colicky abdominal pain	Pain free, irregular bowel habit
6	Ileotransverse anastomosis	2	Four episodes of small bowel obstruction over 1 year	Symptom free
7	Ileotransverse anastomosis	1	Single episode of small bowel obstruction	Technical failure

Results

Clinical response is summarized in *Table 1*. Balloon dilatation failed in two patients with ileotransverse anastomotic recurrence because the endoscopist was unable to intubate the stricture. Both patients subsequently underwent a segmental resection. At laparotomy there was no evidence of perforation. Examination of the resected bowel showed particularly tight and tortuous strictures.

Dilatation was technically successful in the remaining three patients with anastomotic strictures, although it had to be repeated in one because of recurrent obstructive symptoms. Two patients are asymptomatic 21 and 27 months later, and the other has improved greatly after a single dilatation, with only occasional episodes of abdominal pain and without evidence of intestinal obstruction.

The patient with duodenal stenosis improved considerably after four dilatations with 6 kg weight gain, cessation of vomiting and a radiologically confirmed increase in gastric emptying. At 23 months after dilatation he presented with recurrent small bowel disease, eventually leading to a further small bowel resection; at operation a gastroenterostomy was also fashioned.

The patient with the colonic stricture has been dilated twice and remains well 23 months later.

Balloon dilatation was performed on one to four occasions; the total number of procedures was 15. All patients tolerated the procedure well, although one developed abdominal pain and transient fever 48 h after dilatation of an ileotransverse stricture. This resolved with antibiotic therapy.

Discussion

This preliminary series has shown that endoscopic balloon dilatation of intestinal strictures resulting from Crohn's disease is feasible. While the total number of procedures was relatively few, the technique appears safe and was well tolerated. We have extended our experience to over 30 procedures and have yet to encounter a serious complication.

The procedure is sometimes technically demanding; a tortuous endoscope may not freely allow passage of the balloon catheter, strictures may prove difficult to intubate or to broach fully. These factors accounted for two failures. Only a highly selected group of patients are suitable; those with long or multiple strictures and those with lesions inaccessible to endoscopy are clearly unsuitable. Patients with short, fibrous strictures are amenable to this form of therapy and may derive satisfactory improvement. We have not routinely reinvestigated patients following dilatation to minimize radiation risks.

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Blood transfusion and recurrent Crohn's disease

A. D. N. Scott*,
J. K. Ritchie† and
R. K. S. Phillips*†

†St. Mark's Hospital and
**Professorial Surgical Unit,*
St. Bartholomew's Hospital,
London, UK
Correspondence to:
Mr R. K. S. Phillips, Professorial
Surgical Unit, St. Bartholomew's
Hospital, West Smithfield, London
EC1A 7BE, UK

The effect of blood transfusion on the postoperative recurrence of Crohn's disease has been investigated. Clinical and pathological data from 197 patients treated by right hemicolectomy between 1947 and 1988 have been analysed. Symptomatic recurrences confirmed radiologically or histologically have been recorded and cumulative recurrence rates calculated for transfused and non-transfused patients. Perioperative blood transfusion does not influence the development of recurrent disease (log rank test, $\chi^2 = 0\cdot112$).

It is nearly 20 years since the beneficial effect of blood transfusion in prolonging renal allograft survival was first demonstrated[1]. Although the mechanism of this transfusion effect is still not clear[2], it is likely to involve not only specific immunological effects such as clonal deletion[3], stimulation of suppressor T cells[4,5] and the appearance of anti-idiotypic[6] and blocking[7] antibodies, but also a non-specific down-regulation of the immune system[8,9].

More recently it has been suggested that the immunomodulatory effect of blood transfusion can increase the risk of local recurrence of neoplasm[10–13] and infectious complications[14] after surgery for colorectal cancer. The evidence for such an effect on other tumours is less clear[15–20] but there is certainly a greatly increased incidence of malignancy when the immune system is compromised in either immunodeficient[21,22] or immunosuppressed[23,24] patients.

In Crohn's disease a variety of immunological disturbances have been demonstrated[25]. These include alterations in lymphocyte function[26], structural[27] and functional[28] changes in the epithelial cell, the appearance of lymphocytotoxic antibodies[29] and abnormal suppressor cell activity[30,31]. Since immunological mechanisms are likely to be involved in the pathogenesis of the disease it is possible that perioperative blood transfusion could influence the risk of recurrence of Crohn's disease after surgical resection.

Patients and methods

The 241 patients treated by right hemicolectomy for ileocolic or terminal ileal Crohn's disease between 1947 and 1988 at St Mark's Hospital have been reviewed. None of these patients had had a previous resection or bypass. Forty-four patients were excluded from further study, because of postoperative death in two, uncertain pathology in five, known residual disease in 20, no follow-up in five and inadequate transfusion data in 12. Among the remaining 197 patients 92 (47 per cent) were men and 105 (53 per cent) were women; the mean age was 31 years (range 15–62 years). Of these patients 102 (52 per cent) received a transfusion of whole blood or packed cells between 1 week before operation and 1 week after operation; the mean number of units transfused was 2·4 (range 1–8, median 2) and the transfusion was administered intraoperatively in 17 patients, postoperatively (within 24 h) in 11 patients and both intraoperatively and postoperatively in 60 patients. The other 14 transfused patients received blood either before operation or between 2 and 7 days after operation.

All 197 patients underwent right hemicolectomy and were then followed up for a mean of 7·7 years (range <1 to 35 years). Recurrence was defined as the appearance of symptoms and signs suggestive of Crohn's disease together with radiological and/or endoscopic and/or histological confirmation of disease.

Life table analysis[32] was used to calculate the cumulative risk of recurrence in the transfused and non-transfused patients (*Figure 1*) and these were then compared using the log rank test. Statistical significance was otherwise assessed using either the Mann–Whitney *U* test or the *t* test after analysing the distribution of the data.

Results

Table 1 shows that the transfused and non-transfused patients were broadly comparable, although there were significant differences in the preoperative haemoglobin and albumin concentrations. The mean length of small bowel resected was not significantly different in the two groups of patients (45·6 cm in transfused patients *versus* 38·1 cm in non-transfused patients; *t* test, $P > 0\cdot1$). However, the length of large bowel resected was significantly different (20·3 cm in transfused patients *versus* 14·0 cm in non-transfused patients; *t* test, $P < 0\cdot001$)

There was no difference in the length of involved bowel, as measured by the pathologist from the resected specimen, between the transfused (mean 33·6 cm) and non-transfused (mean 30·5 cm) patients. Similarly, in the transfused patients, there was no association between the number of units transfused and the length of involved bowel (*Table 2*).

The distribution of the ABO and Rhesus blood groups in the 197 patients was similar to that for the general population and there was no significant difference in crude recurrence rates between the various blood groups (*Table 3*).

Of the 197 patients, 73 (37 per cent) developed clinical features of recurrent disease, the diagnosis being confirmed radiologically in 52 patients (71 per cent), endoscopically in two (3 per cent) and histologically in 19 (26 per cent). Crude recurrence rates were no different between the transfused and non-transfused patients, with 38 of 102 (37 per cent) transfused patients developing recurrent disease as compared with 35 of 95 (37 per cent) non-transfused patients.

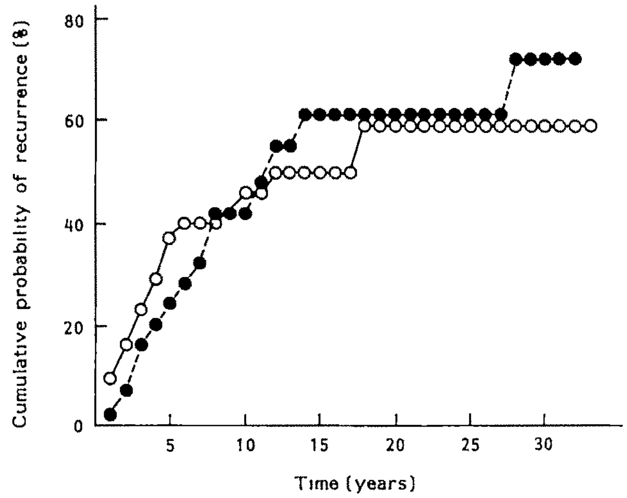

Figure 1 *Cumulative risk of recurrence in transfused (—●—) and non-transfused (—○—) patients. $\chi^2 = 0\cdot112$, n.s.*

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Table 1 *Preoperative patient details*

	Transfused ($n=102$)		Not transfused ($n=95$)		
	Mean(s.d.)	%	Mean(s.d.)	%	Significance
Length of illness (months)	60·6(63·2)	90	61·4(55·1)	93	–
Age (years)	31·2(11·2)	100	31·0(10·3)	100	–
Haemoglobin (g/dl)†	11·7(1·3)	96	12·9(1·4)	97	$P<0·001$ (t test)
White cells ($\times 10^9$/l)†	9·5(3·6)	81	9·2(3·4)	83	–
Lymphocytes (as % white cell count)†	20·3(10·2)	41	22·5(7·9)	45	–
Lymphocytes ($\times 10^9$/l)†	2·0(0·8)	41	2·2(1·2)	45	–
Albumin (g/dl)†	35·5(4·3)	58	37·5(4·4)	68	$P<0·02$ (t test)
Total protein (g/l)†	67·9(7·2)	63	66·0(6·2)	71	–
Requiring steroids (%)‡	37·2	93	33·7	100	$P>0·5$ (χ^2)
Requiring parenteral nutrition (%)	1·1	94	1·1	100	–

* Percentage of total number of patients for whom information was available. Values †at <2 weeks before operation, ‡at time of surgery

Table 2 *Units transfused and extent of disease*

No. of units	No. of patients	Involved bowel (cm)
1	19	36·7(21·5)
2	49	36(23·1)
3	14	29·8(11·4)
4	8	33·4(12·2)
5	3	26·7(14·6)
6	1	10
7	3	41·3(20·1)
8	1	30

In four patients the exact number of units transfused was not known. Values given are mean(s.d)

Table 3 *Blood groups and recurrence*

Blood group	Patients		General population (%)	Crude recurrence (%)
	n	% of total		
A	80	41	42	37·5
B	31	16	9	35·5
O	74	38	46	36·5
AB	11	6	3	36·4
Rh+	163	84	85	
Rh−	32	16	15	

ABO group not known for one patient; Rhesus group not known for two patients

There was also no significant difference in the cumulative rate of recurrence between the transfused and non-transfused patients either over the whole period of follow-up (log rank test, $\chi^2=0{\cdot}112$) or at any time interval after operation (*Figure 1*).

Discussion

In this retrospective study of a large number of patients, all of whom have been treated by the same operative procedure, it has been shown that perioperative transfusion does not influence the risk of recurrence of Crohn's disease after surgical resection. This implies either that recurrence of Crohn's disease is not influenced by immunosuppression or that transfusion does not have the same immunological effects in patients with inflammatory bowel disease that it has in transplant recipients or patients with cancer.

Numerous immunological abnormalities have been demonstrated in Crohn's disease[26,33] and, although many of these may be secondary changes or epiphenomena, the pathogenesis of the condition undoubtedly involves alterations in immunological activity[34]. The aetiology of recurrent Crohn's disease is uncertain. It is likely that Crohn's disease affects the entire gastrointestinal tract from the outset[35,36] even though the presence of inflammation may appear discrete and localized. Recurrence may therefore merely represent the progression of latent pre-existing disease to the level of microscopic or even macroscopic changes. Even so, one might expect that this process would be affected by any alteration in the activity of the immune system. The present results, however, do not support this suggestion.

The immunological effects of blood transfusion in patients with inflammatory bowel disease have not been investigated. Certainly there is evidence that nutritional disturbances[37], treatment with steroids[38] and Crohn's disease itself[39] may all be associated with reduced immunological responsiveness, and all these factors may be relevant in patients requiring surgery for complicated Crohn's disease.

The timing of transfusion may be of critical importance; experimental studies have shown an accelerated rate of tumour growth in animals when allogeneic blood is given before transplantation of a tumour, but no effect is observed if the blood is given at the time of, or after, tumour transplantation[40,41]. Potential renal transplant recipients are transfused before receiving the antigenic stimulus of the allograft and long-term immunosuppression, whereas transfused cancer patients receive blood at the time of surgery, presumably many months after the development of a tumour which may already be associated with immunological impairment[42]. It is therefore likely that the effects of transfusion in transplantation and cancer involve different immunological mechanisms, none of which may be relevant in inflammatory bowel disease.

It should also be noted that in the present study the transfused patients received blood between 1 week before and 1 week after operation. It is possible that some of the patients in the non-transfused group received blood outside this time interval because some had been referred from elsewhere and patients with Crohn's disease may require transfusion at times other than the time of surgery. However, it is the authors' impression that this is infrequently necessary in patients presenting for their first operation for ileocolic Crohn's disease; it is more commonly seen in patients with severe colonic disease and with complicated recurrent disease, but these patients were deliberately excluded from this study.

The results of the study are at variance with those of two others[43,44], both of which have suggested that blood transfusion protects against the development of recurrent disease. However, both of these studies involve a fairly short follow-up of a relatively small number of patients. Sample size and length of follow-up are both particularly important in this context, as there does appear in the early years to be a delay in recurrence in the transfused group (*Figure 1*). However, in the present study this did not reach statistical significance and by 8 years the curves have crossed; we would conclude that blood transfusion confers no advantage in terms of disease recurrence.

After surgery for ileocolic Crohn's disease the risk of symptomatic recurrence is extremely high (approximately 60 per cent at 10 years[4,5]) and the question of a transfusion effect in surgery for Crohn's disease therefore deserves further investigation. Ethical and practical considerations preclude a prospective randomized clinical trial. However, it should be possible to investigate the immunological effect of transfusion in Crohn's disease by preoperative and postoperative *in vitro* tests of mononuclear cell function.

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Limited hepatic resection for selected cirrhotic patients with hepatocellular or cholangiocellular carcinoma: a prospective study

From 1 January 1983 to 1 January 1989 123 cirrhotic patients with hepatocellular cancer (n = *122*) *or cholangiocarcinoma* (n = *1*) *were screened using liver function tests, α-fetoprotein determination, ultrasonography with biopsy (and in selected cases computed tomography or nuclear magnetic resonance), laparoscopy and angiography, Child–Pugh classification and urea-nitrogen synthesis rate. Twenty-three patients were selected for surgical resection because the tumour was smaller than 5 cm, not centrally located and at least 1 cm away from main structures; there was no evidence of multicentricity or metastatic disease; and the Child–Pugh classification was A or B and the urea-nitrogen synthesis rate at least 6 g/day. Upper gastrointestinal endoscopy was used routinely to identify oesophageal varices which were present in 17 cases; ten patients with a history of variceal haemorrhage (43 per cent) had preoperative endoscopic sclerotherapy. In cases with recurrent haemorrhage, surgery was used to prevent intraoperative and postoperative bleeding. Tumour resection was carried out using controlled hypotension and hepatoduodenal ligament clamping. Twelve bisegmentectomies, ten segmentectomies and one atypical resection were performed. The operative mortality rate was 13 per cent with liver failure and sepsis as the causes of death. The 'recurrence rate' was 26 per cent and the late mortality rate for the whole group up to 1 January 1990 was 30 per cent; 13 patients were still alive. The 12-month survival rate was 77 per cent and after 5 years it was 49 per cent. Thus, surgical resection of small liver tumours is the treatment of choice in this selected group of patients.*

**K.-J. Paquet,
P. Koussouris,
M. A. Mercado,
J.-Fr. Kalk, D. Müting
and W. Rambach**

*Department of Surgery and
Medicine, Heinz-Kalk Hospital,
D-8730 Bad Kissingen, Germany
Correspondence to:*
Dr K.-J. Paquet, Heinz-Kalk
Hospital, POB 21 80, D-8730 Bad
Kissingen, Germany

Hepatocellular carcinoma (HCC) remains difficult to detect and has a bad prognosis. Its association with cirrhosis, particularly posthepatic cirrhosis, is clearly recognized and not only in patients with positive hepatitis B serology[1,2]. The widespread use of ultrasonography, computed tomography, nuclear magnetic resonance and α-fetoprotein estimation has allowed earlier discovery of the disease[3,4]. Using these methods routinely small tumours can be detected which can be considered for surgical resection. However, liver resection in patients with liver cirrhosis is not popular. This is due partly to the high operative mortality[5], partly to the poor long term prognosis of the disease[4,6,7] and partly to the belief that carcinoma developing in the cirrhotic liver is multicentric and, hence, unsuitable for surgical treatment[8,9].

In recent years these views have changed radically. Careful selection of patients can lead to an improvement in the results of liver resection in cirrhosis. Nagao *et al.*[7], Okuda *et al.*[8] and Franco *et al.*[10] have shown that the operative risk is acceptable and that resection can improve the survival of these patients, particularly in those with small solitary tumours where there is no portal vein invasion or extrahepatic dissemination.

The purpose of the present study is to review specific aspects of resection of HCC in patients with cirrhosis and portal hypertension with particular reference to selection criteria, new developments in surgical technique, perioperative management, and the results of resection in comparison with those obtained in non-resected patients.

Patients and methods

Patient selection

A total of 123 patients were admitted to the Heinz-Kalk Hospital between January 1983 and January 1989 suffering from hepatocellular carcinoma in a cirrhotic liver. Of these, 23 were selected for surgical resection using the following screening techniques. After taking a clinical history all patients were evaluated by carrying out liver function tests and measuring α-fetoprotein levels Ultrasonography and ultrasonographic guided liver biopsy were then routinely employed. Twenty-two patients had histologically proven HCC and one had a cholangiocarcinoma, henceforth this last patient will be included in the group of HCC patients. Computed tomography and/or nuclear magnetic resonance scanning were performed in doubtful cases Occasionally, laparoscopy was carried out with biopsy under direct vision, because superficial lesions may be missed by the other imaging techniques If an indication for operation was present, an angiographic study was performed.

All patients had their urea-nitrogen synthesis rate measured[11,12] by collecting 24 h urine specimens in thymol under standardized metabolic conditions. They received 60 g protein, 90 g fat and 240 g carbohydrate (8400 kJ). The level of urea-N in the serum of preprandial blood and urine was determined on the first and third days. The quantitative determination of urea in serum and 24 h urine was carried out using the colorimetric urease method (Boehringer, Mannheim, Germany). The urea-nitrogen synthesis rate was calculated according to the formula shown in *Table 1*

The patient's considered for surgery all had good liver function with Child–Pugh's grade A or B classification and a urea-nitrogen synthesis rate of at least 6 g/day (*Table 2*). The tumour was less than 5 cm in

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Table 1 *Formula for the calculation of urea-nitrogen synthesis rate*

$$PU = UUN \times 2{\cdot}14 \times volume + (BUN_2 - BUN_1) \times 0\ 06 \times kg \times F$$

PU = production of urea (g urea/24 h)
UUN = urea nitrogen in urine (g/l)
Vol. = volume of the 24 h urine
BUN_1 = blood urea nitrogen at the beginning of the 24 h urine collection (mg/100 ml)
BUN_2 = blood urea nitrogen at the end of the 24 h urine collection
kg = body weight (kg)
F = factor for the calculation of body fluid
= 0 55 female, 0 60 male
2·8 = factor: conversion from mg/dl into mmol/l

Table 2 *Child–Pugh classification and urea-nitrogen synthesis rate developed and used in Heinz-Kalk Hospital, Bad Kissingen, Germany foi classification of patients with liver cirrhosis and hepatocellular carcinoma*

	Points		
Observations	1	2	3
Nutritional status	Excellent	Good	Poor
Ascites	None	Moderate Easily controlled	Marked Poorly controlled
Neurological disorder (encephalopathy)	None	I–II	III–IV
Serum bilirubin (mg/100 ml)	<2·0	2·0–3·0	>3·0
Serum albumin (g/l)	>35	30–35	<30
Prothrombin concentration (Quick test)	>75%	50–75%	<50%
Urea-nitrogen synthesis rate (g/day)	9–12	6–9	>6

Child–Pugh A = 6–8 points; Child–Pugh B = 9–11 points; Child–Pugh C = 12 or more points

diameter and not located centrally in the liver or less than 1 cm away from a main branch of the portal vein, hepatic artery, biliary duct or hepatic vein. Multicentricity of tumour and metastatic disease were contraindications to surgery Upper gastrointestinal endoscopy was routinely performed and 17 patients (74 per cent) had oesophageal varices. Ten had a history of oesophageal variceal bleeding and all had undergone therapeutic paravariceal endoscopic sclerotherapy In one patient without a history of bleeding large varices (grade III–IV in our classification, see ref. 13) with telangiectasias were found; prophylactic endoscopic sclerotherapy was carried out. One patient rebled three times after sclerotherapy, on two occasions emergency sclerotherapy stopped the bleeding temporarily; after the third recurrence emergency devascularization of the upper two-thirds of the stomach and 4–6 cm of the abdominal oesophagus was performed successfully. Two patients had two recurrences and one patient one recurrence of haemorrhage after therapeutic sclerotherapy, in all cases this was stopped by emergency sclerotherapy. During the following 2–3 weeks, a distal splenorenal shunt was performed in one case and a mesocaval interposition shunt in two cases.

Surgical technique

The following technique was used for tumour resection Sodium nitroprusside was used during operation to reduce systolic blood pressure to 70 mmHg[14] After completely mobilizing the right or left liver lobe, intraoperative ultrasound was used to exclude previously undetected lesions or/and to localize tumour situated under the liver surface and not palpable. The hepatoduodenal ligament was occluded with a tourniquet for 30 min, opened for 5 min and occluded again if resection had not been completed. Finger fracture technique was used in the first ten patients and jet dissection during the last 13 resections, the tumour was resected with a surrounding margin of 1 cm of unaffected liver. When the tumour was located in one or two liver segments, resection of each of the affected segments was performed When the tumour was 2 cm in diameter an 'atypical' resection was performed, such tumours were resected with a surrounding margin of 2 cm of unaffected liver. After removal of the clamps on the hepatoduodenal ligament the resection area was inspected for bleeding vessels which were ligated with fine absorbable sutures The area was then covered with dehydrated fibrin cloth or an omental patch. Drainage of the upper right abdomen was not used so as to avoid an ascitic fistula. Antibiotics were not used routinely. During the postoperative period care was taken to maintain correct fluid balance and avoid encephalopathy.

The survival curve was contructed according to the non-parametric method of Kaplan and Meier[15]

Results

Twelve bisegmentectomies, ten single segmentectomies and one atypical resection were performed. Three patients (13 per cent) died in the first four postoperative weeks due to liver failure (two patients) and sepsis (one). In one case, second laparotomy for rebleeding was necessary. All patients developed ascites in the postoperative period and responded well to conventional therapy. A transient alteration of liver function tests was usually observed in the form of slight hyperbilirubinaemia and high transaminasaemia, with a diminution in serum albumin levels and slight prolongation of prothrombin time. All of these parameters returned to preoperative values after 2–4 weeks.

After discharge from hospital, two patients died because of liver failure in the first postoperative year and five further patients died in the following two (two patients), four, five and six (one patient) years respectively. These five patients developed recurrent HCC. At the time of follow-up on 1 January 1990, 13 patients were still alive after a median interval of 41 months (13–80 months); only one had evidence of tumour recurrence This 73-year-old patient is now being treated by transarterial embolization 32 months after the recurrence. Thus, a 'recurrence rate' of 26 per cent was observed (six of 23 patients; five dead and one alive).

The late mortality for the whole group is 30 per cent (seven of 23). Seven patients are receiving chronic long term endoscopic sclerotherapy. Two of them bled in the postoperative period and were successfully controlled by endoscopic sclerotherapy. The survival curve calculated according to the Kaplan–Meier method is shown in *Figure 1*. The 12 month survival rate is 77 per cent, and the 5-year survival rate 49 per cent.

Discussion

In comparison with quantitative measurement of global liver function using foreign substances such as galactose elimination rate and antipyrine clearance, the daily urea-nitrogen synthesis rate assesses the production of endogenous urea. This method was originally proposed by Rudman *et al.* in 1970 and then by Galambos in 1978[11,12]. Hansen and Poulsen[16] demonstrated that, before and after resection of 70 per cent liver tissue in rats, determination of urea-nitrogen synthesis rate was a more useful assessment than the galactose elimination rate and antipyrine clearance. These results were confirmed in patients with liver cirrhosis by Vilstrup *et al.* in 1988[17] who showed that the

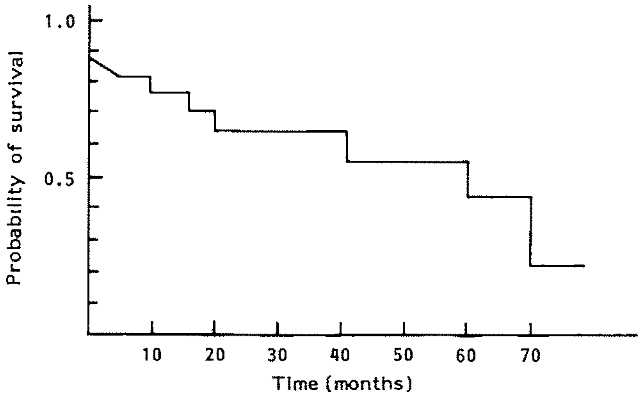

Figure 1 *Survival curve according to the non-parametric method of Kaplan–Meier in 23 patients with liver cirrhosis and hepatocellular carcinoma*

Table 3 *General features of patients with liver cirrhosis and hepatocellular (cholangiocellular) carcinoma* (n = *23*)

	Number	Percentage
Age (years)	63 (55–69)	
Sex	18M/5F	
Type of cirrhosis:		
posthepatic	16	70
alcoholic	7	30
Histological type of hepatic carcinoma		
hepatocellular	22	96
cholangiocellular	1	4
Child–Pugh classification		
A	15	65
B	8	35

standardized urea-nitrogen synthesis rate was a good index of functioning liver mass.

HCC is most frequently observed in patients with liver cirrhosis. Liver resection in such cirrhotic patients is more difficult and hazardous than in patients with an otherwise normal liver. Large resections are poorly tolerated and the patients have a tendency to develop liver failure in the postoperative period[5]. With the selection method described above, morbidity and mortality can be reduced. Patients with an acceptable liver function (Child–Pugh A+B) and hepatic reserve as reflected by the urea-nitrogen synthesis rate have better results than those with poor function[18–21]. The minimum rate of 6 g/day for urea-nitrogen synthesis suggests that patients have a good functional liver mass[16–18]. Small tumours (diameter less than 5 cm) with a favourable localizaion can be safely resected[6,10,19,21,22]. A minimum of 1 cm separation of the tumour from the main liver ducts and vessels allows also a safe resection with an adequate margin of uninvolved liver[6,10,19]. However, in this study on two occasions operation revealed that the tumour was located on the left hepatic vein; resection was performed successfully and both patients are still living after 20 and 44 months respectively without recurrence.

Clamping the hepatoduodenal ligament prevents intraoperative bleeding[14,24]. This procedure is well tolerated by patients with liver cirrhosis who have good liver function. Using the method of clamping described, we did not observe any major complications including variceal haemorrhage and liver failure that could be attributed to the transient block of both portal and arterial hepatic supply. It allowed quick resection with minimal blood loss. This was particularly true for peripherally located tumours well away from the hepatic veins. In more than half of our cases intraoperative blood transfusion was not necessary. When transfusion is needed we now prefer to transfuse autologous blood, withdrawn in the weeks or days before operation.

The use of peritoneal drains in these patients can be dangerous, because they may leak ascitic fluid and cause secondary sepsis. Covering the resection area with dehydrated fibrin or omental patch diminishes the risk of bleeding and biliary leakage and obviates the need for drainage. However, in five patients drains were used and removed on the third (two patients), fifth (two patients) and seventh postoperative day respectively). In four cases the defect in the abdominal wall had to be made watertight in order to stop ascitic leakage.

Seventeen of our patients (74 per cent) had portal hypertension and ten (43 per cent) had a history of bleeding. Such hypertension can be a major cause of morbidity and mortality. To combine liver resection with a shunt operation or devascularization is a demanding operation that is not well tolerated. For this reason we treated the varices by preoperative sclerotherapy and reserved surgery for recurrent bleeding despite sclerotherapy. We recommend that patients with a history of variceal bleeding or those with large varices according to our classification[13] should be treated prophylactically by sclerotherapy[25].

The operative mortality rate observed in our series is 13 per cent. This is slightly higher than that observed in a similar group of cirrhotic patients undergoing portal decompression surgery[26,27]. The main causes of death were liver failure and sepsis. We think that our figure is acceptable in patients with liver cirrhosis undergoing a major hepatic procedure since it is comparable or better than results in other reports[6,8,19,20,28–30] Nevertheless, there are reports of series without mortality[10,23]. We consider that our long term survival rate of 77 per cent at 1 year and about 49 per cent at 5 years, justifies the use of surgery in these selected cases. Such results are better than those achieved following resection of the majority of gastrointestinal carcinomas.

There is no doubt that hepatic resection, if successful, appears to prolong survival[6,7,10,19,28–30]. In a recent publication Okuda's group[31,32] has shown that in 100 consecutive patients the median survival time was 35 months for surgery (34 patients), 28·8 months for transcatheterarterial embolization (20 patients), 10·6 months for intra-arterial chemotherapy (28 patients) and 9·7 months for no treatment (18 patients). A group of 37 patients with Child–Pugh classification A had a median survival time of 37·1 months, 36 with Child B and 27 with Child C had median survival times of 16·2 months and 1·6 months respectively. Our own retrospective analysis of a series of 100 patients investigated from 1977 to 1982 also show a median survival time of 10 months in patients not receiving treatment.

We conclude that patients with small HCC, liver cirrhosis and portal hypertension who fulfil carefully defined criteria may obtain benefit from surgical resection of the tumour. Using the methods outlined for perioperative care and operative management, we believe that resection remains the treatment of choice for such tumours.

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Management of bleeding liver tumours in Hong Kong

A retrospective study was undertaken of 41 patients diagnosed as having suffered spontaneous liver rupture over a 4-year period to identify the clinical features, treatment and outcome of this complication in an area in which hepatocellular carcinoma is endemic. Two patients were excluded with a revised diagnosis of haemorrhagic malignant ascites. Of the remaining 39 patients, 37 bled from ruptured hepatocellular carcinoma, one from peliosis hepatis and multiple liver cell adenomas, and one from a malignant hepatic epithelioid haemangioendothelioma. Analysis showed that 59 per cent of patients were in shock on admission and that all but two of the 37 patients with ruptured hepatocellular carcinoma were men with cirrhosis. The association with cirrhosis was significantly higher than in a series of 45 patients with hepatocellular carcinoma undergoing elective resection during the same period ($P<0.05$). Treatment consisted of supportive care only in two patients, angiographic embolization in four, emergency liver resection in 11 of whom six died, hepatic artery ligation in 12 of whom eight died, and suture and/or packing in eight of whom six died. One patient died at laparotomy and in another patient bleeding was successfully arrested by intratumoural injection of absolute alcohol. Because of the high operative mortality of emergency surgery in these poor risk patients, prospective evaluation of emergency angiographic embolization is required.

G. A. Dewar,
S. M. Griffin, K. W. Ku,
W. Y. Lau and A. K. C. Li

Department of Surgery, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, NT, Hong Kong

Correspondence to:
Professor A K. C. Li

Spontaneous liver rupture with acute haemoperitoneum has several potential causes In Sub-Saharan Africa and the Far East, hepatocellular carcinoma is the main cause, and is the presenting feature in 5–15 per cent of cases[1]. This is in contrast to the West where spontaneous bleeding from hepatocellular carcinoma is an uncommon surgical emergency Indeed, up to 1988 only 14 North American cases of ruptured hepatocellular carcinoma had been reported in the literature[2], while in a UK series the incidence of tumour rupture[3] was only 2·7 per cent This is not surprising because in such low risk regions the age standardized incidence of hepatocellular carcinoma is less than 3 per 100 000 per year, whereas in high risk regions such as Mozambique and South-East Asia it exceeds 100 per 100 000 per year[4]. When spontaneous liver rupture does occur in Western societies, other pathology needs to be considered. This would include peliosis hepatis and liver cell adenomas in oral contraceptive users[5], and rare entities such as bleeding hepatic haemangiomas[6], metastases[7,8], polyarteritis nodosa[9] and even 'normal' liver in eclampsia[10].

In Hong Kong, the treatment of spontaneous bleeding from hepatocellular carcinoma traditionally has been aggressive. Resuscitation has been followed frequently by laparotomy and hepatic resection when feasible[11,12]. When resection is not possible because of advanced cirrhosis, bilobar disease or invasion of the main portal vein or inferior vena cava, alternative surgical measures such as hepatic artery ligation, suture plication, packing and application of haemostatic agents have been employed (either alone or in combination) in an attempt to control bleeding. Many of these patients have underlying posthepatitic cirrhosis with varying degrees of liver decompensation, so that laparotomy, especially in the face of haemorrhagic shock, is poorly tolerated and the prognosis is grave. Emergency angiography embolization would seem to be a reasonable non-operative therapeutic alternative, but has not been practised generally owing to restricted availability Furthermore, there is considerable doubt among surgeons as to its efficacy. We report our experience over the past 4 years in managing spontaneous bleeding from liver tumours.

Patients and methods

A retrospective review was undertaken of all patients treated at the Prince of Wales Hospital, Shatin, Hong Kong for spontaneous liver rupture over the 4-year period May 1985 to May 1989 Although 41 patients were initially identified from the records, two patients were excluded from further analysis with a revised diagnosis of haemorrhagic malignant ascites Abdominal paracentesis in these two patients had revealed heavily blood-stained fluid, but they remained haemodynamically stable on observation so that major tumoural rupture was considered unlikely The remaining 39 patients form the basis of this report Ruptured hepatocellular carcinoma was responsible for bleeding in 37 (95 per cent) patients while two had tumour rupture from other pathology The diagnosis of hepatocellular carcinoma was made histologically in 24 patients and on the basis of an elevated α-fetoprotein level in 13 cases α-Fetoprotein was measured by enzyme immunoassay and was considered diagnostic of hepatocellular carcinoma if raised above 500 ng/ml During the same period, 45 patients underwent elective hepatic resection for hepatocellular carcinoma of a total of 380 patients treated for this disease at our hospital This represents a spontaneous rupture rate of 9 7 per cent, and an elective resection rate of 11 8 per cent

All patients who underwent emergency surgery were operated on by members of the admitting surgical team, which included surgeons in training As such, therapeutic decisions regarding the choice of haemostatic intervention were made individually by several surgeons of varied experience according to general guidelines referred to in the introduction, but without rigid adherence to a predefined treatment protocol In particular, patient allocation to non-operative treatment by emergency angiographic embolization depended primarily on the immediate availability of a skilled radiologist experienced in interventional angiography

Past medical history, demographic details, presenting features, investigations, treatment and outcome were recorded Shock on admission was arbitrarily defined as a pulse rate of >100 beats per min and a systolic blood pressure of <100 mmHg. Special note was made of the presence or absence of liver cirrhosis, as well as the hepatitis B virus surface antigen status and preoperative α-fetoprotein levels when available In those patients submitted to emergency surgery, operative findings were reviewed and included tumour details (size, multifocality, source and site of bleeding) as well as the method employed to achieve haemostasis. Haemostatic measures were regarded as successful when ongoing transfusion requirements were <4 units of blood and when vital signs remained stable. Morbidity, outcome and autopsy findings when available were noted. For the purpose of this review, operative mortality was defined as death within 60 days of presentation or during the same hospitalization.

Statistical analysis where appropriate was performed using Student's *t* test, and survival probabilities were estimated by the Kaplan–Meier method[13].

Results

Following the exclusion of two patients as previously mentioned, 39 patients with spontaneous massive bleeding from liver tumours were studied. Bleeding was from ruptured hepatocellular carcinoma in 37 of these patients, from a ruptured epithelioid haemangioendothelioma of the liver in one patient[14] and from peliosis hepatis and multiple liver cell adenomas in another. The age range of the 37 patients with ruptured hepatocellular carcinoma was 30–96 years (median 56 years), and all except two (i.e. 95 per cent) of these patients were men.

Acute abdominal pain was the chief complaint in 38 patients. The remaining patient was found unexpectedly at elective right hepatectomy (for an 8 cm right lobe hepatocellular carcinoma) to have haemoperitoneum and tumour disruption before surgical manipulation. Fourteen patients gave a history of having collapsed at home, while a further 12 gave a history of dizziness. A history of previous ill-health was obtained in only eight patients (duration 2 weeks to 4 months). Four patients were known to have hepatic malignancy before their index admission for bleeding, while a further four were known to have oesophageal varices and had received injection sclerotherapy.

Thirteen (33 per cent) patients were clinically jaundiced on admission. All had a variable degree of abdominal distension. Twenty-three (59 per cent) patients were in hypovolaemic shock on admission. One patient was misdiagnosed before operation as having a perforated peptic ulcer but was found to have a bleeding left lobe hepatocellular carcinoma at emergency laparotomy.

Laboratory findings on admission supported the clinical impression that many of these patients had advanced disease with a variable degree of liver decompensation. Hyperbilirubinaemia (range 1–409 μmol/l, median 42 μmol/l) was present in nearly half of the patients and hypoalbuminaemia (range 21–41 g/l, median 30 g/l) in the rest. Thirty-two (82 per cent) patients were found to be seropositive for hepatitis B virus surface antigen, while α-fetoprotein was elevated above 500 ng/ml in 27 (69 per cent).

Thirty-six of 37 (97 per cent) patients with ruptured hepatocellular carcinoma were considered to have underlying cirrhosis of the liver, the diagnosis of which was made on the basis of macroscopic appearances at laparotomy (25 patients), or confirmatory histology (12 patients). Bleeding was from the right lobe of liver in 19 of 37 (51 per cent) patients, from the left lobe in 11 (30 per cent), and was unspecified in seven (19 per cent). Twenty-four of 37 (65 per cent) patients had bilobar disease on presentation as documented by laparotomy findings (19 patients), ultrasound examination (three patients) or hepatic angiography (two patients).

All except six of the 39 patients were operated on. In two patients no active intervention was undertaken because of poor liver reserve and extreme frailty, and only supportive care was given. Six patients underwent emergency angiography with a view to selective transarterial tumoural embolization. Selective cannulation failed in one patient for technical reasons, while another was assessed as having a potentially resectable unilobar tumour following diagnostic injection. The latter patient subsequently underwent emergency right hepatectomy without embolization. Four patients were embolized with Ivalon® (Prince of Wales Hospital, Hong Kong) particles and metal coils. Extravasation of contrast from the bleeding lesion before embolization was demonstrable in only one patient. Nevertheless, bleeding was successfully stopped in all four of these patients, and all four recovered sufficiently to be discharged.

Eleven patients underwent emergency hepatic resection (*Table 1*). There were six right hepatectomies, two left hepatectomies and three non-anatomical resections. Ten of these 11 patients had cirrhosis, and five were in shock on admission. The operative mortality rate for emergency resection was 55 per cent (6 of 11) and only four patients survived for longer than 4 months. It is of interest that one patient died from recurrent haemoperitoneum 3 months after an emergency left lateral segmentectomy, and was shown to have both hepatic remnant and peritoneal recurrent disease at autopsy.

Twelve patients were managed by hepatic artery ligation, and in three (25 per cent) of these patients suture plication of the bleeding lesion was also performed. The operative mortality rate for this procedure was 67 per cent (8 of 12). Three of these patients survived for 6 months, but died of liver failure.

One patient died at laparotomy from exsanguination shortly after the abdomen was opened but before any haemostatic measure could be applied. Eight patients were managed by operative suture plication and/or packing, with an operative mortality rate of 75 per cent (6 of 8). Two patients in whom the bleeding lesion had merely been sutured survived for 4 months.

One patient, a 37-year-old man with cirrhosis who presented in shock, was found at emergency laparotomy to have bilobar hepatocellular carcinoma and active bleeding from a right lobe

Table 1 *Emergency resection for ruptured hepatocellular carcinoma over the 4-year period 1985 to 1989*

Age (years)	Shock	Cirrhosis	Tumour size (cm)	Procedure	Outcome	Cause of death
61	–	+	6	R hepatectomy	Died 4 months	Remnant recurrence with liver failure
60	–	+	10	R hepatectomy	Died 24 h	Bleeding
47	–	+	14	R hepatectomy	Alive 1 month	—
65	–	+	6	R hepatectomy	Died 20 h	Bleeding
47	–	–	10	R hepatectomy	Died 6 months	Remnant recurrence with liver failure
68	–	+	10	R hepatectomy	Died 5 days	Myocardial infarction
50	+	+	20	L hepatectomy	Died on table	Bleeding
55	+	+	5	L hepatectomy	Alive 7 months	—
75	+	+	6	Segmentectomy II and III	Died 10 days	Liver failure, haemoperitoneum
45	+	+	5	Segmentectomy	Died 3 months	Liver and peritoneal recurrence
68	+	+	3	Segmentectomy II and III	Died 6 days	Liver failure

All patients were men. –, absent; +, present

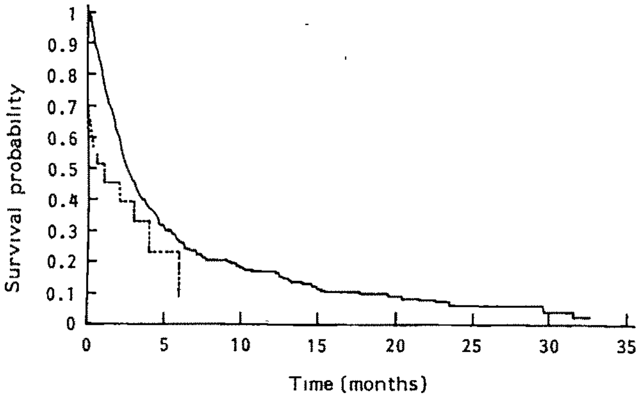

Figure 1 *Survival curves of patients with hepatocellular carcinoma* ——, *no rupture* (n = *343*), - - -, *rupture* (n = *37*)

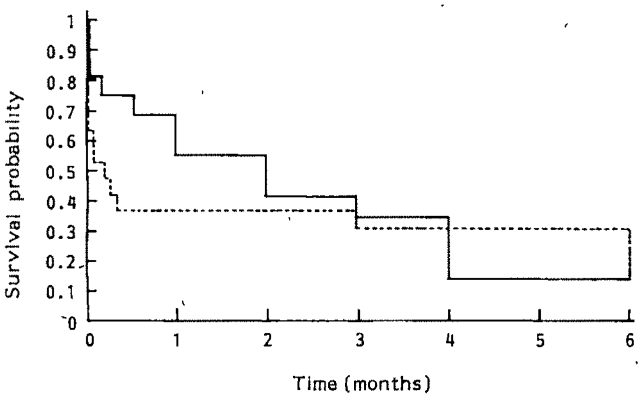

Figure 2 *Survival curves of patients with bleeding liver tumours divided into 'shock'* (n = *23*) *and 'no shock'* (n = *16*) *groups. Log rank test comparison is not appropriate owing to cross-over of curves*[13] ——, *no shock,* - - -, *shock*

lesion. Bleeding was successfully stopped by intratumoural injection of 50 ml of absolute alcohol; right hepatic arterial ligation was not possible because of tumour infiltration.

Only four patients in this series are currently alive (follow-up 2–8 months). All four have hepatic remnant recurrent disease, while one has pulmonary metastases *Figure 1* shows the Kaplan–Meier survival curves of ruptured and non-ruptured hepatocellular carcinoma in patients treated at our hospital during the study period, while *Figure 2* depicts the survival curves of patients with bleeding liver tumours divided into 'shock' and 'no shock' groups In *Figure 1* it can be seen that the estimated median survival time for ruptured hepatocellular carcinoma was <1 month. Exsanguination was the main cause of death in the approximately 50 per cent of patients who died within the first week, whereas remnant recurrence with liver failure was high in the remaining 50 per cent expected to survive beyond 1 week. Altogether only eight (20 per cent) patients survived for ⩾4 months. Analysis of *Figure 2* indicates that patients in shock on presentation were at particular risk of early death, their estimated median survival being about 2 days compared with 2 months for patients not in shock.

Discussion

Hepatocellular carcinoma is a common disease in Hong Kong where it is the second commonest cause of death from malignancy[15]. Typically it occurs in patients with established posthepatitic cirrhosis who are seropositive for hepatitis B virus. Unfortunately the vast majority of these patients in Hong Kong are already symptomatic and incurable at the time of presentation[16] This disease was the cause of spontaneous liver rupture in all but two patients in the present series, and tumour rupture was the presenting feature in 9·7 per cent of patients treated for this neoplasm at our hospital. This figure is only slightly lower than the 14·5 per cent incidence of tumour rupture noted in an earlier Hong Kong series[12], and is comparable to three other Asian series where incidences of 5·5 per cent[17], 7 per cent[18] and 12·4 per cent[19] were recorded

It is noteworthy that only a minority of patients gave a previous history of ill-health[20] Despite this, 36 of 37 (97 per cent) patients with ruptured hepatocellular carcinoma were considered to have cirrhosis Admittedly the criteria for diagnosis of cirrhosis were lenient in that histological confirmation was obtained in only 12 (32 per cent) patients. Nevertheless, this almost invariable association of ruptured hepatocellular carcinoma with underlying cirrhosis of the liver contrasts significantly with our elective resection series, 71 per cent of whom had cirrhosis ($P < 0.05$). Although there was also a higher percentage of men in the emergency group (95 per cent compared with 87 per cent), this difference was not statistically significant. In this series ruptured hepatocellular carcinoma was an entity encountered almost exclusively in men with cirrhosis (35 of 37 or 95 per cent). Similar findings have been noted in a large Thai series[18], but in three other Asian series the association with cirrhosis and male sex, although present, was less striking[12,15–16]. The implication of this finding is that cirrhosis (presumably because of complicating portal hypertension and/or coagulopathy) and male sex (possibly because of robust physical activity or hormonal influences) appear to be factors relevant to the mechanism of tumour rupture Venous hypertension secondary to obstruction of the draining hepatic veins of the tumour by thrombi, together with a rich and fragile arterial supply, may be important factors in this respect[18,19].

Histological confirmation of hepatocellular carcinoma was obtained in only 23 of 37 (62 per cent) patients despite 31 (84 per cent) having undergone laparotomy. This probably reflects hesitancy on the part of the attending surgeon to biopsy a tumour which had been the source of bleeding, and also reflects difficulty in obtaining consent for autopsy in Hong Kong.

It is important to appreciate that bleeding from ruptured hepatocellular carcinoma is not always exsanguinating, nor necessarily progressive Minor rupture may manifest as haemorrhagic malignant ascites, and two additional patients were initially identified but subsequently excluded from our series with this revised diagnosis. Furthermore, we found that hypovolaemic shock was present in only 23 of 39 patients on presentation. We believe now that the absence of shock on presentation is an important favourable prognostic factor (see *Figure 2*), a point which has not been emphasized previously. Provided that vital signs are maintained and delay is minimal, expeditious ultrasonography can be performed to help decide on the choice of interventional therapy. Crucial information may thus be obtained as to the potential resectability of the bleeding lesion, despite the fact that emergency resection is rarely appropriate. In addition, we believe that the combination of shock and cirrhosis should alert the attending surgeon to the realization that laparotomy (let alone hepatic resection or arterial ligation) will be tolerated poorly. This is supported by the observation that on presentation many of these patients have evidence of significant hepatic decompensation

The fact that 80 per cent of patients with ruptured hepatocellular carcinoma in this series died within 4 months of presentation attests to the grave prognosis of this complication when managed by surgeons of varied experience. In the past we and others have been enthusiasts of emergency resection when feasible However, our own experience dictates caution; histologically clear margins were obtained in only two of the 11 emergency resections in the present series. The operative mortality rate for emergency resection was 55 per cent. Remnant recurrence occurred in all survivors, the longest of whom is alive with remnant disease at 7 months. Two previous reports[12,17] included emergency resections in 13 and 14 patients respectively. These resections were mostly palliative, and were accompanied by operative death rates of about one-third. On the other hand, each of these series[12,16] had a

5-year survivor, one of whom had cirrhosis. It is because of such long-term survival, albeit rare, that enthusiasm for selective resection still prevails. The concept of achieving haemostasis by preliminary transarterial embolization so as to allow subsequent elective resection in these cases is attractive[21], but was not practised by us.

Hepatic artery ligation[18] was a poor treatment method in this study, the operative mortality rate being 67 per cent. Although haemorrhage was successfully arrested in all 12 patients subjected to surgical ligation of the relevant feeding artery, eight of them died from postoperative liver failure. We believe that this poor outcome reflects the cirrhotic liver's inability to withstand the stress of ischaemia and surgery, and that this contrasts strongly with our early favourable results achieved by angiographic embolization. Indeed, bleeding was successfully controlled without hospital mortality in all four patients treated by the latter method. We are aware of the limitations of this observation in the context of a retrospective study. Patient numbers are small and there is the possibility of selection bias according to disease severity (for instance only one of these patients was shocked on presentation). Nevertheless we feel that the demonstrated extremely poor life expectancy of our patients when treated surgically justifies further evaluation of embolization. We have subsequently embarked on a prospective study of emergency angiographic embolization as the initial therapeutic measure. The results of three other groups[22–24] support an initial radiological approach to what has traditionally been regarded as a surgical problem, provided that adequate blood volume replacement is supervised by the surgeon before and during the procedure.

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Prevention of postoperative renal dysfunction in patients with obstructive jaundice: a multicentre study of bile salts and lactulose

J. A. Pain, C. J. Cahill*, J. M. Gilbert†, C. D. Johnson‡, J. E. Trapnell§ and M. E. Bailey¶

*King's College Hospital, London, *Westminster Hospital, London, †Royal Victoria Hospital, Bournemouth, ‡Southampton General Hospital, Southampton, §Royal Victoria Hospital, Bournemouth, and ¶Royal Surrey County Hospital, Guildford, UK*

Correspondence to:
Mr J A. Pain, Department of Surgery, Brook General Hospital, Shooters Hill, London SE18 4LW

The role of preoperative lactulose and bile salts in the prevention of postoperative renal failure in patients with obstructive jaundice has been evaluated in a prospective randomized trial. One hundred and two patients undergoing surgery for obstructive jaundice (bilirubin >100 µmol/l) were randomized into three groups: those receiving preoperative oral lactulose (n=35), those receiving oral sodium deoxycholate (n=32) and a control group of patients receiving no specific treatment (n=35). All patients received intravenous fluids commencing the night before surgery. One patient in the control group and none in the treatment groups developed postoperative renal failure. Postoperative deterioration of renal function in patients with normal preoperative function was significantly more common in the control group than in the treatment groups ($\chi^2=8{\cdot}1$, d.f.=2, $P<0{\cdot}02$). The incidence of renal failure and impairment was lower in this control group than that reported in previous studies. This may be due to the introduction of adequate preoperative hydration. Additional protection occurs by the preoperative administration of either lactulose or sodium deoxycholate.

Patients with obstructive jaundice have an increased incidence of postoperative renal failure[1,2]. Systemic endotoxaemia, resulting from increased absorption of intestinal endotoxin into the portal blood[3,4] and its spillover into the systemic blood due to impaired removal by the hepatic reticuloendothelial system[5,6], may be important aetiological factors. Preoperative oral bile salts and lactulose have been shown in preliminary studies[7,8] to reduce systemic endotoxaemia and to protect postoperative renal function. A prospective randomized multicentre study has been performed to evaluate these agents.

Patients and methods

One hundred and fourteen patients from six hospitals were entered into the study at least 3 days before undergoing surgery for relief of obstructive jaundice. All patients had a plasma bilirubin level >100 µmol/l. Patients about to undergo preoperative percutaneous external or endoscopic internal drainage, with a previous history of renal or parenchymal liver disease, or who had been given a general anaesthetic in the preceding 6 weeks were excluded. Twelve patients (three controls, three in the lactulose group and six in the bile salt group) failed to comply with the protocol requirements and were withdrawn: seven had inadequate sample collection, three underwent non-operative relief of jaundice and two underwent laparotomy alone.

The remaining 102 patients were evaluated. Thirty-five patients received preoperative oral lactulose, 32 patients received preoperative oral sodium deoxycholate, and 35 patients acted as controls and received neither treatment. All patients received preoperative intravenous fluids commencing the night before surgery. Patients were given perioperative mannitol and antibiotics according to the preference of the individual surgeon.

A comparison of the three groups is shown in *Table 1*. Patients receiving lactulose were older and had a higher mean bilirubin level than patients in the other groups. Diagnoses and operative details are shown in *Table 2*.

Lactulose

Oral lactulose (Duphalac®, Duphar Labs Ltd, UK), 30 ml 6-hourly, was given for 3 days before surgery. The final dose was administered within 12 h of surgery. If a patient developed troublesome or frequent diarrhoea (>4 times per 24 h) the subsequent dose of lactulose was omitted and doses thereafter were halved.

Bile salts

Sodium deoxycholate, the bile salt with the greatest antiendotoxic action[9], was used in this study. Sodium deoxycholate (Kochlight Ltd, UK) was made up into 250 mg capsules. Patients received 500 mg by mouth 8-hourly for 2 days before surgery. The final dose was given within 12 h of surgery.

Table 1 *Patient details*

	Control group (*n*=35)	Lactulose group (*n*=35)	Bile salt group (*n*=32)
Age (years)			
Mean	69(10)	74(8)	66(11)
Range	54–86	32–86	42–86
Sex (M:F)	24:11	25:10	24:9
Jaundice duration (days)	22 (13)	21(14)	20(12)
Diabetes (*n*)	1	3	4
Bilirubin (µmol/l)	317(156)	358(165)	270(110)
Alkaline phosphatase (units/l)	711(313)	584(256)	623(363)
Transaminase (aspartate aminotransferase) (units/l)	146(63)	129(61)	121(118)
Albumin (g/l)	33·1(6)	31·2(8)	34·0(6)
Haemoglobin (g/dl)	12·3(1)	12·3(2)	12·6(2)
Preoperative blood transfusion (*n*)	1	2	2
White cell count (10^9/l)	9·1(3)	8·5(3)	9·7(5)
Perioperative mannitol (%)	71	51	59
Perioperative antibiotics (%)	89	97	94

Values given are mean(s.d.) unless otherwise stated

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Table 2 *Diagnoses and operative details*

	Control group (n=35)	Lactulose group (n=35)	Bile salt group (n=32)
Diagnosis			
Carcinoma of the pancreas	21	28	14
Malignant duct obstruction	3	2	7
Carcinoma of the gallbladder	3	1	0
Choledocholithiasis	6	3	8
Benign bile duct stricture	0	0	3
Pancreatitis	2	1	0
Operative details			
Palliative bypass	26	31	19
Pancreatectomy	0	1	0
Stent insertion	3	0	5
Exploration common bile duct	6	3	8
Operative duration (min)*	98(35)	97(32)	113(39)
Presence of liver metastases (%)	31	20	9

* Values given are mean(s.d.)

Renal function

Serial 24 h endogenous creatinine clearance measurements (C_{24}) were performed on the 2 days before surgery and on the first 3 days after operation. Impairment of renal function was defined as a preoperative C_{24} value of <40 ml/min associated with a raised plasma urea and creatinine level, or a >20 per cent fall in mean C_{24} value after operation[7,8,10]. Renal failure was defined as a urine volume <400 ml/24 h associated with a rising plasma urea and creatinine level

Statistical analysis

Comparison of changes in creatinine clearance were made with analysis of variance Comparisons of the incidences of renal impairment were made with the χ^2 test.

Results

Twelve patients (34 per cent) had modification of lactulose dosage because of diarrhoea. Sodium deoxycholate doses were omitted in two patients (6 per cent) because of vomiting and in one patient (3 per cent) because of epigastric discomfort.

Mortality and morbidity

There were five postoperative deaths (within 30 days of operation) in the control group, five in the group receiving lactulose and one in the group receiving bile salts. Causes of deaths and complications are shown in *Table 3*. Renal failure was not a principal cause of death in any patient. Twenty-six per cent of patients had postoperative septic complications and 5 per cent had postoperative gastrointestinal haemorrhage.

Renal failure

One patient in the control group, who had preoperative renal impairment (C_{24} = 38·3 ml/min), developed postoperative renal failure (urine output 320 ml/24 h). This responded to supportive therapy and he was eventually discharged home on the 46th day after operation. No patient receiving lactulose or bile salts developed postoperative renal failure.

Renal impairment

The incidence of preoperative and postoperative renal impairment is shown in *Table 4*. In patients who had normal renal function before surgery postoperative renal impairment was more common (χ^2 = 8·1, d.f. = 2, P < 0·02) in the control group than in the two treated groups (*Table 4*) Overall the C_{24} value in the control group rose from a mean(s.d.) of 63·4(24·2) ml/min before surgery to 64·5(27·7) ml/min after surgery (2 per cent increase). In the group receiving lactulose the C_{24} value rose from 53·4(21·6) ml/min to 61·5(22·1) ml/min (15 per cent increase). In the group receiving bile salts the C_{24} value rose from 63·5(21·1) ml/min to 68·0(19·9) ml/min (7 per cent increase) There were no statistically significant differences between or within groups.

Discussion

An overall 9 per cent incidence of renal failure has been reported in patients with obstructive jaundice[1,2]. In this study only one patient (<3 per cent) in the control group developed renal failure and this resolved Dawson[11] found that in non-jaundiced patients undergoing surgery the maximum fall in C_{24} level after operation was 22·8 per cent. We therefore used a mean postoperative C_{24} fall of >20 per cent as a criterion of renal impairment. The incidence of impairment in the control group was 34 per cent compared with over 50 per cent in the control groups of our earlier studies[3,7,8]. This may be due to the fact that all patients, including the control group, received preoperative intravenous fluids starting at least the day before surgery. Williams *et al.*[12] observed that fatal acute postoperative renal failure in jaundiced patients was preceded by a period of hypotension. The postoperative mortality rate fell from 13 to 7 per cent if patients were routinely transfused before surgery Two possible explanations for this response are a reduction in peripheral vascular resistance[13,14] and a fall in total body water[15] associated with obstructive jaundice.

In patients who had normal preoperative renal function there was a significantly (P < 0·02) greater incidence of postoperative renal impairment in the controls compared with the treated groups (*Table 4*) Additional protection of renal function can be provided by lactulose or bile salts. We have previously shown that lactulose and sodium deoxycholate

Table 3 *Postoperative mortality and morbidity (number of patients)*

	Control group (n=35)	Lactulose group (n=35)	Bile salt group (n=32)
Deaths	5	5	1
Myocardial infarction	–	2	–
Chest infection	3	1	1
Anastomotic leak	–	1	–
Recurrent jaundice	–	1	–
Carcinomatosis	1	–	–
Cardiac failure	1	–	–
Major complications	5*	1	3*
Gastrointestinal bleed	3	1	1
Septicaemia	1	–	2
Subphrenic abscess	–	–	1
Pancreatitis	1	–	–
Biliary fistula	1	–	–
Cerebrovascular accident	1	–	–
Renal failure	1	–	–
Minor complications	6	7	6*
Respiratory infection	1	4	4
Urinary tract infection	1	2	1
Wound infection	3	–	3
Diarrhoea	–	1	–
Prolonged ileus	1	–	–

* Some patients had more than one complication

Table 4 *Overall incidence of preoperative and postoperative renal impairment*

	Control group (n=35)	Lactulose group (n=35)	Bile salt group (n=32)
Preoperative alone	7	10	6
Preoperative and postoperative	4	4	3
Postoperative alone	8*	1	2

* P < 0·02 control group *versus* lactulose and bile salt groups

reduce the incidence of portal and systemic endotoxaemia in patients with obstructive jaundice undergoing surgery[7,8]. Measurement of endotoxins in plasma is a difficult technique requiring great care in obtaining, treating and assaying samples. Because this was a multicentre study these points could not be controlled adequately, therefore measurements were not undertaken.

Lactulose, a commercially available synthetic disaccharide, is used in the treatment of constipation and for the prevention of hepatic encephalopathy. Lactulose reduces endotoxaemia in parenchymal liver disease[16–18], and in a non-randomized study of patients with obstructive jaundice lactulose was shown to reduce endotoxaemia and protect against postoperative renal failure[8]. The mechanism of action is unknown. It has a direct antiendotoxic action *in vitro* and in animals[8,19] but this is more modest than that of bile salts[9]. It may reduce the availability of colonic endotoxin for absorption by its laxative effect[20] and its alteration of colonic bacterial flora[21]. If lactulose is absorbed from the intestine of jaundiced patients it may exert a systemic action Many of the toxic effects of endotoxin are mediated via the release from macrophages of effector substances such as tumour necrosis factor[22], and lactulose has been shown to modify this macrophage response[23].

Bile salts are detergents and inactivate the endotoxin molecule *in vitro*[24–26]. The presence of bile within the intestinal lumen reduces endotoxin absorption into the portal blood. Endotoxin absorption is increased in obstructive jaundice[3] or following external biliary drainage[27], but endotoxin absorption is reduced if oral bile salts are administered[3], or if internal biliary drainage is performed[28].

The choice of the correct bile salt appears to be important. In patients with obstructive jaundice oral sodium deoxycholate prevents both portal and systemic endotoxaemia and protects postoperative renal function[7]. Chenodeoxycholic acid is less effective[10] and ursodeoxycholic acid confers no benefit[28] Sodium deoxycholate has the greatest detergent activity, and has the most effective antiendotoxic action *in vitro* and *in vivo*[9].

The incidence of postoperative renal failure in patients with obstructive jaundice is reduced by adequate preoperative hydration. Preoperative administration of lactulose or sodium deoxycholate confers additional protection. Lactulose is widely available and safe, but in the doses used in this study may cause diarrhoea requiring dose reduction. Sodium deoxycholate is not commercially available. Clinical experience of its use is limited, but no serious side-effects have been observed.

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Long-term results of choledochoduodenostomy in the treatment of choledocholithiasis: assessment of 225 cases

P. Parrilla, P. Ramirez, F. Sanchez Bueno, J. M. Perez, M. F. Candel, M. S. Muelas and R. Robles

Department of Surgery, Hospital Virgen de la Arrixaca, University of Murcia, Murcia, Spain

Correspondence to:
Dr P. Ramirez, Servicio Cirugia General (3a planta), Hospital Virgen de la Arrixaca, 30120 El Palmar, Murcia, Spain

During a 10-year period 2610 patients were operated on for biliary lithiasis; in 225 (8·6 per cent) cases the operation concluded with a choledochoduodenostomy. The commonest preoperative diagnosis (62·2 per cent) in these 225 patients was choledocholithiasis; 30 patients had previously had a cholecystectomy. After choledochoduodenostomy, 4·0 per cent of patients had an intra-abdominal complication; six patients developed an intra-abdominal abscess and three developed an external biliary fistula. Four patients (1·8 per cent) died, three from pulmonary complications and one from a biliary fistula. After a mean follow-up period of 4·6 years, 71·5 per cent of patients were asymptomatic. The remainder suffered from dyspepsia (15·1 per cent), colicky pain (8·7 per cent) or episodes of cholangitis (4·7 per cent). Endoscopy in the symptomatic patients allowed the following conclusions: (a) no patient with dyspepsia had a problem at the anastomosis; (b) 27 per cent of those with colic had anastomotic stenosis or the sump syndrome; and (c) all patients with cholangitis had anastomotic stenosis and residual calculi.

The usefulness of supraduodenal choledochoduodenostomy as a biliary bypass technique after bile duct surgery for choledocholithiasis has been controversial for many years[1–5]. Following Riedel's first description in 1888[6], the technique was practised progressively in continental Europe, but met with strong resistance in the UK and USA, until publications by Sanders[7], Hurwitz and Degenskein[8], Madden *et al* [9] and others presented it as a safe and efficient technique.

Although most surgeons include choledochoduodenostomy in their therapeutic armamentarium and consider it a technique indicated in certain cases of choledocholithiasis, it is still controversial in terms of its indications. There is also discussion on the long-term appearance of the sump syndrome[4,10–13] and duodenogastric bile gastritis[4,14] in patients who have had a choledochoduodenostomy.

The aims of the present study were: (1) to review the present indications for supraduodenal choledochoduodenostomy in our unit; (2) to analyse the frequency of postoperative complications and to estimate the perioperative mortality rate; and (3) to study the long-term clinical outcome of the operation by assessing the incidence of the sump syndrome, bile gastritis, cholangitis and reoperation for anastomotic stenosis or retained or recurrent calculi.

Patients and methods

In the period from January 1979 to December 1988, a total of 2610 patients with cholelithiasis were operated on. Surgical exploration of the common bile duct was indicated when the intraoperative cholangiographic study suggested choledocholithiasis, an absence or delay in the passage of contrast agent into the duodenum, or dilatation of the common bile duct to at least 1 cm in diameter. Choledochoduodenostomy was indicated when the bile duct was more than 12 mm in diameter. In 591 (22·6 per cent) of these 2610 patients it was considered necessary to open the common bile duct, and in 225 cases the operation was concluded with a supraduodenal choledochoduodenostomy. Choledochoduodenostomy was therefore performed in the course of operation for cholelithiasis in 8·6 per cent of patients.

The mean age of the patients having choledochoduodenostomy was 66·6 years, 72·5 per cent were over 60 years old. Sixty-seven (29·8 per cent) were men and 158 (70·2 per cent) were women.

Operations were performed for the following preoperative diagnoses: simple cholelithiasis with no suspicion of pathology of the common bile duct ($n=26$); acute cholecystitis due to calculi ($n=26$); choledocholithiasis associated with gallbladder stones ($n=110$), choledocholithiasis in previously cholecystectomized patients, i.e. retained calculi ($n=30$), acute pancreatitis with biliary lithiasis ($n=33$). Cholelithiasis was diagnosed in all cases by ultrasonography which revealed a dilated bile duct in 121 (53·8 per cent) cases. It is important to note that 64 (28·4 per cent) of the patients operated on had serum bilirubin levels of over 85 μmol/l and ten (4·4 per cent) patients had sepsis.

Intraoperative cholangiography was performed routinely. In only 14 of the 225 patients, all operated on as emergencies, was this procedure omitted. In all cases in which intraoperative cholangiography was performed, there was a dilated bile duct of over 12 mm in diameter, accompanied by images suggesting choledocholithiasis in 192 cases, difficulty in the passage of contrast material to the duodenum in 73, and a stone impacted in the papilla in 28.

Calculous material was found in 206 patients (single stones in 63 and two or more stones and/or biliary sludge in the remaining 143). In the remaining 19 patients no material was extracted from the bile duct.

In all patients a supraduodenal external choledochoduodenostomy was performed, basically following Flörcken's technique[15]. Anastomosis was performed in a single layer, generally with 3/0 absorbable stitches. Subhepatic drainage near the anastomosis was used. The time taken to perform the choledochoduodenostomy ranged from 10 to 20 min.

During the study period a further nine patients had a sphincterotomy carried out at the papilla[16] because of impacted stones. The minimum sphincter length sectioned was 10 mm in these cases.

Results

Short-term: operative morbidity and mortality rates

The overall morbidity rate for the series was 21·3 per cent (48 cases). There were 23 wound abscess, 15 pneumonias and one case of thromboembolism. The percentage with intra-abdominal complications was 4·0 per cent (nine cases). There were six intra-abdominal abscesses (four subphrenic, two

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subhepatic) which required surgical drainage, and three external biliary fistulae due to dehiscence of the choledochoduodenal anastomosis. Two of the patients with biliary fistula were cured with conservative treatment, but the third developed multiorgan failure and died after reoperation for biliary peritonitis.

The mortality rate for the series was 1·8 per cent (four patients). The patient with biliary fistula (above) and another three patients aged over 70 years died. Two of these three patients died after symptoms of sepsis secondary to bilateral bronchopneumonia. The third patient showed symptoms of massive pulmonary thromboembolism shortly before discharge from hospital. The mean length of hospital stay after operation was 11·6 days.

Long-term follow-up

Of the 225 patients, 172 (76·4 per cent) were reviewed at between 1 and 9 years (mean 4·6 years) after operation and 123 (71·5 per cent) were found to be totally asymptomatic. In 26 patients there was occasional postprandial discomfort in the upper abdomen without colicky pain (dyspeptic syndrome), 15 reported repeated colicky pain, and the remaining eight patients had been admitted to hospital on various occasions for episodes of cholangitis.

In the eight patients with cholangitis, endoscopy showed an anastomotic stenosis (diameter <3 mm) and endoscopic cholangiography showed choledocholithiasis. Six of these patients underwent reoperation (four at 1 year after the original operation, and the remaining two at 6 and 7 years respectively). Four patients had a wider choledochoduodenostomy fashioned, and in the other two a hepatojejunostomy was performed. The cholangitic episodes in the remaining two patients resolved with medical treatment, and the patients refused reoperation.

Patients with dyspeptic syndrome or colicky pain also underwent endoscopy to assess the diameter of the anastomosis and the existence of food debris in the bile duct (*Table 1*).

In the 26 patients with dyspepsia only three cases of bile gastritis (endoscopic and histological diagnoses) were found which could be connected with the choledochoduodenostomy Another eight patients had diagnoses of mild oesophagitis with hiatal hernia ($n=6$), Barrett's oesophagus ($n=1$), and gastric carcinoma ($n=1$). These pathologies might explain the patients' symptoms but they had no apparent relationship with the choledochoduodenostomy. Endoscopic exploration was normal in the final 15 patients, who were presumed to have functional dyspepsia or irritable colon syndrome.

In the 15 patients with colicky pain, endoscopy revealed four cases of bile gastritis, two cases of bile duct bezoars which were extracted endoscopically, and two cases of stenosis of the choledochoduodenostomy with a diameter of less than 5 mm. In one patient an oesophageal diverticulum was found, and in the remaining six cases endoscopic examination was normal.

Discussion

One of the controversial aspects in bile surgery is how to complete the operation when the common bile duct has been explored through a choledochotomy. There are three possibilities: (a) choledochorrhaphy over a T tube; (b) transduodenal sphincterotomy or sphincteroplasty (with choledochorrhaphy over a T tube or transcystic drainage); and (c) supraduodenal choledochoduodenostomy.

The basic criterion indicating the need for a choledochoduodenostomy is a dilated bile duct of more than 12 mm in diameter[1,11,16,17–21]. Choledochoduodenostomy is also the preferred technique when reoperating on a patient for recurrent or retained stones[1,2,17,20,22]. Also, since the publication of several series of choledochoduodenostomies with little morbidity or mortality[1,3,7–10,13,18,23], the technique has become considered safe and easy, leading to a widening of indications and an increase in its use. For example, when the common bile duct is slightly dilated (8–12 mm) some authors recommend using it in certain circumstances· when there are doubts about the total clearance of the duct[10,24]; when there is intrahepatic lithiasis[4], and when there is suppurative cholangitis[3].

When the common bile duct is dilated (>12 mm), choledochoduodenostomy, with papillary surgery only in those cases where there is an impacted stone which cannot be extracted by choledochal incision, is desirable When the bile duct is normal in size we do not perform this technique because the possible anastomotic width is too small. After opening and clearing the common duct, the choledochotomy is closed over a T tube and papillary surgery is performed only in situations in which it is indicated (impacted stone, papillary stenosis). When the bile duct is slightly dilated (8–12 mm) our aim is to clear the duct with a choledochoscope and to conclude the operation by closing the choledochotomy over a T tube. As before, papillary surgery is required for impacted stones or papillary stenosis. The introduction in our unit of routine choledochoscopy in 1985 has reduced the requirement for papillary surgery and the frequency of residual stones has decreased[25].

The anastomotic stoma must be wide enough to ensure good biliary drainage and prevent stenosis, a main factor favouring cholangitis and recurrent lithiasis[11,26–28]. A longitudinal incision is performed in the bile duct as near as possible to the duodenum, so that the infra-anastomotic bile duct is as short as possible, thus preventing the sump syndrome[13] The incision in the duodenum is made along its longitudinal axis, perpendicular to the choledochal incision. It is recommended that the anastomosis be performed with absorbable suture, which may cause less inflammatory reaction. Another important detail for preventing anastomotic stenosis is to achieve a good apposition between the choledochal and duodenal mucosae[12]. Lastly, we must emphasize that when there is excessive friability of the choledochal and duodenal structures, or when it is difficult to mobilize the duodenum (factors that play an important role in the dehiscence of the choledochoduodenal anastomosis[16]), the technique of choledochoduodenostomy should be abandoned.

The present series agrees with others that more than 70–80 per cent of patients with choledochoduodenostomy are completely asymptomatic 5 years after operation[3,4,10,13]. The proportion of patients presenting with some kind of symptomatology in the long term ranges from 5 to 18 per cent[3,4,10,11,27]. In the present series this was 28 5 per cent.

The dyspeptic syndrome without colicky pain could be

Table 1 *Endoscopic findings and reoperations on symptomatic patients*

	Endoscopic finding				
Syndrome	Bile gastritis	Choledochoduodenostomy stenosis	Choledochal bezoar	Choledocholithiasis	No of reoperations
Dyspepsia ($n=26$)	3	0	0	0	0
Colicky pain ($n=15$)	4	2	2	0	0
Cholangitis ($n=8$)	0	8	0	8	6

connected, as a choledochoduodenostomy complication, with bile reflux gastritis[4,14] or with the sump syndrome[10–13]. However, in this series bile gastritis was demonstrated in only three out of 26 patients, without any of them presenting with obstruction of the distal bile duct. We must consider that associated pathology not related to the choledochoduodenostomy is responsible for most of the dyspepsia.

Colicky pain with or without dyspepsia and without cholangitis must be related to residual calculi due to stenosis at the stoma, or to the sump syndrome. In this series we found this pathology in 27 per cent of patients Some of these sporadic crises of pain were unable to be explained.

The cholangitic crises were connected in 100 per cent of the cases with residual calculi due to stenosis of the neostoma.

The patients with episodes of cholangitis or colicky pain had an endoscopy to assess the diameter of the choledochoduodenostomy, and cholangiography was performed in all cases. If there is marked stenosis of the choledochoduodenostomy with secondary formation of calculi, surgery to reconstruct the anastomosis should be undertaken. Endoscopic papillotomy is considered of little use, because biliary stasis is related to the supra-anastomotic bile duct and not to that situated between the anastomosis and the papilla.

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Endoscopic sphincterotomy: the whole truth

M. E. Lambert,
C. D. Betts, J. Hill,
E. B. Faragher*,
D. F. Martin and
D. E. F. Tweedle

*Departments of Surgery and Radiology, Gastroenterology Unit and *Department of Medical Statistics, University Hospital of South Manchester, Nell Lane, West Didsbury, Manchester M20 8LR, UK*

Correspondence to
Mr D E. F Tweedle

An 8 year experience of 602 patients (median age 76 years) referred for endoscopic management of common bile stones is reported. No patient referred for treatment has been excluded. A diagnostic cholangiogram was achieved in 94 per cent and sphincterotomy was accomplished in 91·5 per cent. The bile ducts were demonstrated to be completely cleared of stones in 491 (81·6 per cent) of 602 patients. A mean number of 1·9 endoscopic retrograde cholangiopancreatography examinations per patient were necessary to achieve this result. Complications of endoscopic sphincterotomy, which were strictly defined, occurred in 10·5 per cent of patients although five patients had two complications (total complication rate 11·3 per cent). The 30-day mortality rate was 2·2 per cent, seven of 13 deaths (1·2 per cent) occurring as a direct result of sphincterotomy. There have been statistically significant improvements in bile duct clearance and complication rates with increasing experience of endoscopists.

In the 10 years after the first procedure , endoscopic sphincterotomy for the removal of gallstones from the bile ducts was performed in more than 50 000 patients[2]. Reported success rates are high and complication rates low, but both these entities must be carefully defined[3]. In some studies, sphincterotomy is considered to be the successful end-point whether or not stones are cleared, and success may approach 100 per cent[4,5]. Others define success as the clearance of stones, giving rates of about 85 per cent[3,6] A factor influencing results is the exclusion of some patients; for example, those in whom cholangiography cannot be achieved, those with a Polya gastrectomy, or those with bile duct stones that are considered too large for extraction Although the number of patients excluded for these reasons may be small, even small alterations to any patient population may have startling effects on results[7].

Similarly, the complications and mortality rates associated with endoscopic sphincterotomy have been variously defined. Most early reports exclude non-endoscopic complications such as myocardial infarction and bronchopneumonia[4,8,9]. Most recent reports have included all deaths occurring within 30 days (the criterion adopted in surgical studies)[10,11]. Confusion may arise if complication rates are calculated for each endoscopic procedure, some patients requiring repeat endoscopy so that the morbidity and mortality rates based on numbers of patients are higher than those based on numbers of procedures.

Patients and methods

To present an accurate evaluation of endoscopic sphincterotomy, we have analysed the results and complications in all patients referred to our unit for endoscopic stone removal between January 1981 and December 1988 Only one patient was not accepted, in this case a Roux-en-Y reconstruction rendered the papilla inaccessible Polya gastrectomy is not a contraindication in our experience and these patients are included. In all cases considered successful, duct clearance was confirmed radiologically. Although the first endoscopic sphincterotomy was performed at this hospital in 1977, we have analysed our experience from 1981, as both clinicians carrying out the procedure were by then experienced in the technique

Indications and results were recorded at the time of each procedure and all patients were followed up for at least 30 days When endoscopic retrograde cholangiopancreatography (ERCP) failed, the presence of stones was demonstrated at subsequent surgery in 17 and by a variety of radiological techniques in 16 All endoscopy was performed by one of two clinicians (D F M. and D E F T) using standard methods[12]. All patients undergoing diagnostic or therapeutic ERCP were given intravenous antibiotics, most recently mezlocillin 2 g, 30 min before endoscopy

Haemorrhage complicating endoscopic sphincterotomy was strictly defined as a fall in haemoglobin concentration of 2 g/dl or more Acute pancreatitis was present when typical pain was accompanied by a serum amylase concentration of >1000 units/l

Statistical methods

The proportions of patients found to fall into various predefined subgroups were assumed to be random samples from the wider population of all patients undergoing endoscopic sphincterotomy The 95 per cent confidence intervals for these proportions were thus estimated assuming a binomial distribution Where valid, proportions were compared using a contingency table analysis, if the proportions were grouped by year of operation, the χ^2 statistic was partitioned to provide a test for the presence of a linear trend over time[13]

Results

Most (89 per cent) of the 602 patients were referred from other hospitals (358 by surgeons and 178 by physicians), the remaining 66 were referred by general practitioners Two hundred and ten (35 per cent) were men, with a median age of 74 years (range 36–94 years), and 392 were women, median age 77 years (range 18–95 years). Two hundred and thirty-three (38·7 per cent) were jaundiced, 220 (36·5 per cent) still had their gallbladders and 61 (10·1 per cent) had clinical evidence of cholangitis Fourteen patients were referred with acute pancreatitis and ERCP was performed during the acute episode Successful clearance of the duct often required more than one attempt; our policy was to repeat ERCP until the ducts were cleared or surgical intervention, usually due to complications or the realization that the stones were too large for endoscopic removal, was deemed necessary In total, 1136 procedures were required (a mean of 1·9 per patient), with a maximum of seven before clearance was achieved.

In four patients the duodenum was never reached, because of an oesophageal stricture in one, hiatus hernia in one, pyloric stenosis in one and failed endoscopic intubation in one

Of 18 patients with a Polya gastrectomy, the papilla could not be located in ten but the ducts were cleared in eight. Previous surgery to the papilla had caused such distortion of the duodenum in six patients that cholangiography was not possible, and in a further 16 cannulation was thwarted by duodenal diverticula. In all, cholangiography failed in 36 (6·0 per cent, 95 per cent confidence interval 4·2–8·2 per cent)

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In 12 of the 566 patients in whom cholangiography was successful, it was immediately apparent that the stones were too large for endoscopic removal and no attempt at sphincterotomy was made. In six, it was impossible to carry out endoscopic sphincterotomy. Sphincterotomy was achieved in 551 patients: more than 99 per cent of those in whom it was attempted, but only 91·5 per cent of the 602 patients referred (*Table 1*).

The ducts were eventually cleared in 491 patients, 89 per cent of those in whom it was attempted but only 81·6 per cent of the original 602. There were several reasons for failure to clear the ducts. In nine patients, the endoscopist decided after several attempts that the stones were too large to remove endoscopically and all eventually underwent surgery. Complications occurred in 12 before complete clearance of the duct could be achieved. Fatal medical conditions (malignancy, renal failure and stroke) interrupted the treatment in nine. In 14 patients further endoscopic attempts would have been feasible but the referring surgeon decided that surgical intervention was preferable. Four very frail patients with large stones had biliary stents positioned around the stones[14]; three patients declined further endoscopy to ensure clearance and one patient was lost to follow-up. For the purposes of this report, these patients have been regarded as failures of treatment. There was a statistically significant improvement in the rate of successful stone extraction over the study period (*Table 2*), although apparently a linear trend, much of the improvement observed occurred between 1982 and 1983. There were coincidental steady and significant reductions in the complication and operation rates over the same period.

Complications

Sixty-eight complications (11·3 per cent; 95 per cent confidence interval 8·8–14·3 per cent) occurred in 63 patients (10 5 per cent; 95 per cent confidence interval 8·5–13·2 per cent) (*Table 3*). Blood transfusion was required in 17 of 29 such patients; ten patients underwent surgery for haemorrhage and two died. One patient who required transfusion suffered myocardial infarction while hypotensive but recovered.

Acute pancreatitis occurred in 16 patients and prolonged the time in hospital (normally 24 h) by a mean of 5 days (range 3–12 days) in those who recovered. Two patients died, one of whom had acute pancreatitis on referral and succumbed to a pancreatic abscess 20 days after successful duct clearance.

Acute cholangitis occurred in 12 patients, with one death, and acute cholecystitis in one patient was successfully treated conservatively. Four patients suffered retroperitoneal perforation, the diagnosis being made radiologically by the detection of free gas on the film which is taken routinely at the end of the procedure, three were silent, but one patient also developed acute pancreatitis and a collection of bile was drained at operation. All recovered.

One patient was found on recovery from sedation to have suffered a dense hemiplegia, but had not been hypotensive nor had she bled. A basket became impacted around a stone in the duct of a morbidly obese, jaundiced man with septicaemia; an operation was necessary to disimpact the basket and remove the stone but he later died from septicaemia. One patient had a cardiac arrest during intubation but was fully resuscitated. One patient with a history of heart disease had a myocardial infarction 5 days after ERCP; she recovered fully One patient who had a stent inserted temporarily to bypass a large stone was found at repeat ERCP to have passed the stone, but it was not possible to remove the stent; this patient remains free of symptoms. In all, 14 patients required urgent surgery for complications and four died. There was a slight numerical trend

Table 1 *Endoscopic removal of stones success rates for endoscopy, cholangiography, sphincterotomy and duct clearance*

	Number of patients	Percentage	95 per cent confidence interval
Patients referred	602		
Papilla of Vater identified	588	97·7	96 1–98 7
Cholangiogram obtained	566	94 0	91 8–95·8
Sphincterotomy performed	551	91·5	89·0–93·5
Ducts cleared	491	81·6	78·3–84 7

Table 3 *Details of complications occurring in 63 patients*

	Number of complications
Bleeding	29
Acute pancreatitis	16
Acute biliary sepsis	13
Perforation	4
Stroke	1
Cardiac arrest	1
Myocardial infarction	2
Impacted Dormia basket	1
Stent lodged	1
Total complications	68 (11 3%)
Patients	63 (10·5%)

Table 2 *Effect of increasing experience on success and complication rates*

	1981	1982	1983	1984	1985	1986	1987	1988
Patients	52	52	96	82	74	88	84	74
Procedures	98	88	191	160	139	182	160	118
Duct clearance								
n	41	33	78	63	67	74	72	62
%	79	63	81	77	91	84	86	84
95% confidence interval	65–89	49–76	72–88	66–85	81–96	75–91	76–91	73–91
							Trend $\chi^2 = 6\ 404$, $P = 0\ 011$	
Complications								
n	7	9	13	9	6	8	7	4
%	13	17	14	11	8	9	8	5
95% confidence interval	6–26	8–30	7–22	5–20	3–17	4–17	3–16	1–13
							Trend $\chi^2 = 5{\cdot}846$, $P = 0\ 016$	
Operations								
n	11	16	17	13	6	6	9	6
%	21	31	18	16	8	7	11	8
95% confidence interval	11–35	19–45	11–27	9–26	3–17	3–14	5–19	3–17
							Trend $\chi^2 = 16\ 508$, $P = 0\ 001$	

Percentages are expressed in terms of numbers of patients

Table 4 *Deaths within 30 days of endoscopic sphincterotomy*

	Number of patients
Acute pancreatitis	2
Bleeding	2
Acute biliary sepsis	3
Impacted Dormia basket	1
Renal failure	1
Hepatic failure	1
Stroke	1
Pneumonia	2
Total	13 (2·2%)

for complications to occur less often after repeat ERCP; 43 occurred in 602 patients during ERCP I (7·1 per cent; 95 per cent confidence interval 5·2–9·5 per cent), 16 in 305 patients during ERCP II (5·2 per cent; 3·0–8·3 per cent) and five in 125 patients during ERCP III (4·0 per cent; 1·3–11·2 per cent) Because of the way in which the data were collated, a formal statistical comparison of these rates was not possible. Examination of the confidence intervals, however, suggests that the trend observed was probably not significant.

Deaths

There were 13 deaths, 2·2 per cent (95 per cent confidence interval 1·2–3·6), within 30 days (*Table 4*), seven as a direct result of endoscopic sphincterotomy. One patient died of pancreatitis with which she was referred and a second patient referred with hepatic failure due to longstanding hepatic disease unrelated to lithiasis died 2 days after duct clearance. A patient in renal failure died 2 days after renal transplantation 20 days after endoscopic sphincterotomy and a fourth suffered a fatal stroke in another hospital 9 days after endoscopic sphincterotomy. Another two died of pneumonia, at home, 12 and 28 days after uneventful endoscopic sphincterotomy.

Discussion

In this study we have attempted to produce a complete and unbiased appraisal of our success in removing stones from the bile ducts after endoscopic sphincterotomy. Our study differs from most others in that we have included all patients referred. Most have evaluated only patients in whom ERCP was achieved[6,8,10]. We found ERCP to be impossible in 6 per cent of patients referred to us and so could attempt sphincterotomy in only 94 per cent. For this reason our results may appear less impressive than some. However, we achieved endoscopic sphincterotomy in 99 per cent of those in whom it was attempted, which compares favourably with other reports[15].

Endoscopic sphincterotomy was achieved at the first attempt in 87 per cent, at the second in 97 per cent, at the third in 98 per cent and at the fourth in 99 per cent. Few published reports indicate the number of endoscopic attempts required to achieve success. It is often possible to perform endoscopic sphincterotomy on a second occasion when it was impossible at the first attempt In some patients this has been achieved after performing a 'pre-cut' with a needle-knife on the first attempt[16]. We remain enthusiastic about the use of this technique[17].

In all successful patients we confirmed that the ducts were clear of stones, if necessary by repeat ERCP. In about half there was no doubt that the ducts were clear immediately after extraction, but in many patients repeat ERCP was necessary. We have not regarded as successes those in whom clearance was not confirmed. Quoted figures for successful duct clearance may include only patients in whom stone extraction was attempted and exclude those in whom it was not, often because of large stones. Stones thought to be too large for endoscopic extraction were encountered in 12 of our patients, all of whom were considered failures of management. At present we manage these large stones with biliary stents, mechanical lithotripsy and extracorporeal lithotripsy, and we hope to be able to reduce the need for choledochotomy because of failed endoscopic extraction.

Comparison of the reported incidence of complications is difficult because the definitions of complications are not given[6,8,11,18]. Haemorrhage has been variously defined as all patients with haematemesis or melaena after endoscopic sphincterotomy[10], haemorrhage requiring transfusion, and haemorrhage requiring more than three units of blood to be transfused[19]. Haemorrhage is the most common complication to follow endoscopic sphincterotomy, occurring in 5–11 per cent of patients[8,19,20]. Bleeding is often seen endoscopically at the time of sphincterotomy and may obscure vision, but this does not usually produce signs or symptoms. By our criterion (a fall in haemoglobin of >2 g/dl), this complication occurred in 29 patients (4·8 per cent of patients, but only 2·6 per cent of endoscopic procedures). In studies that include definitions[10,19], acute pancreatitis is defined by the presence of abdominal pain and a serum amylase level >1000 units/l The same definition was used in this series. Acute pancreatitis was not as common as bleeding in our experience, but two of 16 patients died Acute pancreatitis complicated the first attempt at endoscopic removal in 12 cases (2·0 per cent at ERCP I) but occurred after the second or subsequent endoscopy in only four (0·9 per cent at ERCP II–VII). It seemed to result from difficult or prolonged attempts at cannulation of the common bile duct with repeated filling of the pancreatic duct more commonly than from enlarging the sphincterotomy. Thus, there is no evidence to suggest that, if a patient suffers this complication at the first ERCP, it will occur after subsequent procedures.

Biliary sepsis was the complication with the highest mortality rate, in that three of the 13 patients died. The incidence of postendoscopic cholangitis and cholecystitis (2·2 per cent) was low compared with that of other series[19–24] and possibly reflects our use of systemic antibiotic prophylaxis in all patients[15]. Although we recognized that perforation had occurred in four patients, it was clinically silent in three. In view of this, the true incidence may be higher than realized We always take a film at the end of the procedure to assess this[25]. Repeated procedures may be necessary before the ducts are cleared and, if complications are calculated per endoscopy, the figure will be less than if considered per patient In this series, a mean of 1·9 endoscopies per patient was required so that the complication rate per procedure was about half that expressed per patient.

There was a steady increase in the rate of successful stone extraction until the last 3 years when an increasing number of complex cases were referred, many of these patients had undergone unsuccessful ERCP elsewhere It seems that, as is the case with surgical technique, it takes many years of practice to achieve optimal individual performance; both endoscopists had 3 or more years experience of ERCP in 1981 when this study started. Inevitably, the results of endoscopic choledocholithotomy will be compared with those of surgical removal. The difficulties involved in such a comparison have already been emphasized[3]. Many patients were referred for endoscopy by surgeons who considered them to have unacceptable operative risks; few studies of surgical stone removal indicate the number of patients excluded on this basis. It may be this, rather than simply a difference in expertise, which accounts for the variation in the mortality rate of 2·1–7·4 per cent reported in surgical cases[26–29]. It is probable that if all the elderly, jaundiced patients in this series had undergone surgical stone removal the mortality rate would have been much higher. Although the risk factors for surgery have been assessed[30], as yet little attention has been paid to risk factors for endoscopic choledocholithotomy. Our own[31] and others'[32,33] experience suggests that there is a difference between the factors influencing the risks of the two techniques.

After apparently successful endoscopic choledocholithotomy, the duct system is usually 'swept' with a basket or a balloon and a number of films are examined If any doubt about the completeness of extraction remains, the patient usually undergoes a check ERCP a month or so later, or a nasobiliary catheter can be left *in situ* for duct perfusion[34]. Despite this, stones cannot be cleared in about 10 per cent of patients. A similarly thorough examination of the duct immediately after surgical exploration is difficult and the rate of successful clearance of 87–89 per cent reported in recent series[26,29,35–37] barely compares with the success of endoscopic sphincterotomy, and at apparently greater cost in terms of mortality and morbidity in elderly patients.

A controlled trial of endoscopic *versus* surgical choledocholithotomy, including all patients with stones in the common bile duct, has never been performed. From the data now available, such a trial is probably unnecessary and unethical. What is required is increased precision in defining the risks involved in each technique for individual patients. We believe that such patients should be assessed by the surgeon, endoscopist and interventional radiologist working in close liaison, and the decision as to surgical or endoscopic removal should be made on clinical grounds.

In common with other centres, our commonest cause of failure in patients in whom we achieved cholangiography was a large stone above the relatively narrow lower segment of the common bile duct. This series consisted of patients undergoing endoscopic choledocholithotomy before the introduction of extracorporeal shock wave lithotripsy and electrohydraulic lithotripsy in this hospital. With the introduction of these facilities, we are certain that our success rate will improve further[38].

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Adrenaline injection for endoscopic haemostasis in non-variceal upper gastrointestinal haemorrhage

R. J. C. Steele, K. G. M. Park and T. J. Crofts

Department of Surgery, University of Aberdeen, Aberdeen, UK

Correspondence to:
Mr R. J. C. Steele, Floor E,
West Block, University Hospital,
Queen's Medical Centre,
Nottingham NG7 2UH, UK

Over a 30-month period, 53 patients with actively bleeding non-variceal lesions of the oesophagus, stomach or duodenum were treated by endoscopic injection of 1/10 000 adrenaline. Initial haemostasis was obtained in 50 cases, and permanent haemostasis in 44. Emergency surgery for bleeding was required in nine patients overall, and there were four deaths. All lesions requiring surgery were located on the posterior wall of the duodenum or the lesser curve of the stomach, and all but one had evidence of an exposed arterial vessel. Adrenaline injection is an effective, safe and simple method of endoscopic haemostasis.

Although endoscopic injection therapy for the control of variceal bleeding is well established[1] its use in peptic ulcer bleeding is relatively recent. Various agents have been used including ethanol[2], the sclerosant polidocanol[3], and a combination of adrenaline and polidocanol[4]. Adrenaline injection alone is also effective[5], and a controlled trial from Hong Kong has shown significant benefit from this approach[6].

In the present report, we describe our experience of adrenaline injection in a consecutive series of patients with actively bleeding non-variceal lesions of the upper gastrointestinal tract. Careful documentation of the endoscopic appearances and other relevant data was carried out for each patient in an attempt to define those who would be most likely to respond to the treatment.

Patients and methods

During a 30-month period, 53 patients with non-variceal actively bleeding lesions of the upper gastrointestinal tract were treated by local injection of adrenaline delivered at the time of initial endoscopy. These patients were referred from medical wards for possible surgical therapy or from surgical wards specifically for endoscopic treatment. The time between admission and referral was highly variable. There were 31 men and 22 women, and their ages ranged from 24 to 91 years with a mean of 65. Of the patients, 27 (51 per cent) were shocked, as defined by a systolic blood pressure of less than 100 mmHg and a pulse rate of over 100 per minute, and the mean haemoglobin level was 8.6 g/dl with a range of 5.9 to 12.0 g/dl. Twenty-five patients had serious concurrent disease which was deemed to put them at high risk from operative intervention (*Table 1*).

In each case endoscopy was performed using an Olympus 1T-20 (Keymed, Southend, UK) endoscope under midazolam sedation or, exceptionally, general anaesthesia; continuous ECG and blood pressure monitoring was employed for all patients. Any suspected source of bleeding was washed vigorously through the washing channel of the endoscope to clear away blood and loose clot, and in no instance was arterial bleeding precipitated by this manoeuvre. The lesion was a peptic ulcer in all cases except one oesophageal Mallory–Weiss tear and one pancreatic cancer invading the duodenal wall. There were 27 duodenal ulcers, 17 gastric ulcers, three stomal ulcers and four ulcers in a hiatus hernia or lower oesophagus. The exact positions of these lesions are shown in *Table 2*. The endoscopic appearances were classified as active arterial bleeding (spurting vessel), oozing or oozing with a visible vessel. The distribution of these endoscopic stigmata is shown in *Table 3*.

The bleeding point or oozing area was injected with 1 ml aliquots of 1/10 000 adrenaline using an NM-1K (Olympus) flexible needle injector up to a total of 10 ml or until the bleeding stopped. Repeat endoscopy was routinely carried out within 24 h and further injection performed if active bleeding was seen. Clinical rebleeding, defined as fresh haematemesis or melaena associated with hypotension or tachycardia was taken as an indication for immediate surgery. Oral intake was commenced immediately after a satisfactory repeat endoscopy.

Results

Initial haemostasis was achieved in 50 of the 53 patients. Three required emergency laparotomy after unsuccessful injection; two had massive bleeding from the gastroduodenal artery in the posterior wall of the duodenum making adequate endoscopic visualization impossible, and one had diffuse bleeding from an inoperable pancreatic carcinoma invading the duodenal wall. Six patients were found to have further active bleeding at elective repeat endoscopy within 24 h, and all of these were successfully reinjected, although one subsequently required surgery. Six patients had clinical rebleeding and were subjected to operation.

There were four deaths in the series. The patient with inoperable carcinoma of the pancreas invading the duodenum died immediately postoperatively. A 54-year-old man died from pulmonary embolism 16 days after underrunning of a gastric ulcer, a 79-year-old man with severe obstructive airways disease died 5 days after truncal vagotomy and pyloroplasty from respiratory failure, and a 54-year-old woman died 24 days after successful injection of a benign gastric ulcer as a result of disseminated malignancy. There were no significant local or systemic complications of adrenaline injection although, in both of the patients with oesophageal lesions, marked transient hypertension was observed during the injection. This was not seen in any other patient.

Excluding the patient with pancreatic carcinoma, all of the other eight patients who required surgery had peptic ulcers on

Table 1 *Concurrent illness in patients with actively bleeding lesions of the upper gastrointestinal tract*

Condition	Number
Chronic obstructive airways disease	7
Ischaemic heart disease	5
Cardiac failure	2
Anticoagulant therapy	4
Cardiac valvular disease	3
Obesity	5
Incisional hernia	1
Hemiplegia	1
Liver metastases	1
Hodgkin's disease	1
Mental retardation	1

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Table 2 *Distribution of bleeding lesions*

Site	Number
Oesophagus	
lower third	2*
Stomach	
hiatus hernia	3
fundus	0
stoma	3
greater curve	1
lesser curve	10 (4)
antrum	6
First part duodenum	
anterior	4
antero-superior	4
superior	2
postero-superior	3
posterior	6 (3)
postero-inferior	2 (1)
inferior	5
antero-inferior	1
Second part duodenum	1† (1)

Numbers in parentheses indicate those requiring emergency surgery. All lesions were peptic ulcers except *one Mallory–Weiss tear and †one pancreatic carcinoma

Table 3 *Site and endoscopic appearance of bleeding lesions*

	Endoscopic appearance			
Site	Arterial bleeding	Oozing	Oozing + visible vessel	Total numbers
Oesophagus	2	0	0	2
Hiatus hernia	3	0	0	3
Stomach	6	6	5	17
Stoma	2	1	0	3
Duodenum	13	11	4	28
Total	26	18	9	53

the posterior aspect of the duodenum or on the lesser curve of the stomach (*Table 2*). All had active arterial bleeding or oozing associated with a visible vessel (*Table 3*) and all but one had been shocked before endoscopy as compared with only 43 per cent of other patients. There were no differences between the patients requiring surgery and those who did not in terms of age, sex or lowest haemoglobin level before endoscopy.

Discussion

Leung and Chung first described the use of adrenaline injection for endoscopic haemostasis in active non-variceal upper gastrointestinal haemorrhage in 1987[5]. Since then, a controlled trial by the same group has demonstrated a significant benefit from this technique in terms of need for surgery, amount of blood transfused and time spent in hospital[6]. Last year, the initial experience of adrenaline injection in the UK was reported[7], and of 15 patients with active arterial bleeding permanent haemostasis was achieved in 13. In the present series, we attempted to treat all patients with active bleeding, and emergency surgery was required in 17 per cent with an overall mortality of 7·5 per cent.

When considering this mortality rate it must be emphasized that all subjects had active bleeding at the time of endoscopy, as it is known that around 15 per cent of such patients are likely to succumb with conventional treatment[8] The study group also represents a particularly high risk group of patients for surgical intervention in view of the large number with concurrent disease[9]. Three of the nine patients requiring an operation died in the postoperative period, and it is unlikely that endoscopic therapy increased the risks of surgery as undue delays did not occur.

In assessing the results, it is also important to take the type of bleeding into account. From the control groups of trials of endoscopic therapy, it is known that emergency surgery is required in only about 24 per cent of patients with non-arterial bleeding, whereas it is necessary in at least 59 per cent of those with arterial bleeding and in 38 per cent of those with non-bleeding visible vessels[9]. In our present study, 19 per cent (5 of 26) of patients with arterial bleeding and 5·5 per cent (1 of 18) of those with oozing alone required surgery Out of nine patients with oozing and a visible vessel, however, three (33 per cent) came to surgery. The positions of the lesions which needed surgical treatment is also of interest as all were either on the posterior wall of the duodenum or on the lesser curve of the stomach. This is in keeping with the findings of Swain and others[10], and may be of value in predicting those patients who will not ultimately respond to endoscopic therapy.

There were no complications attributable to the adrenaline injections in this series, although the hypertension seen in the patients with oesophageal lesions is worthy of note. It is probable that injection into the oesophagus introduces adrenaline directly into the systemic circulation so that first-pass extraction by the liver does not occur. Despite the apparent safety of this technique, we consider continuous ECG and blood pressure monitoring to be mandatory, and appropriate equipment and expertise for resuscitation must be available in the endoscopy room.

Several different methods of endoscopic haemostasis are now available, including laser photocoagulation, electrocoagulation, heater probe and injection therapy. The relative merits of these techniques have been recently reviewed[8], and there is no clear answer as to the ideal method. Injection, however, has the attraction of requiring no expensive extra equipment, and it does not pose any special technical difficulty to an experienced endoscopist. Various substances are available for injection; good results have been obtained using the sclerosants ethanol and polidocanol in uncontrolled studies[2,3], and a randomized controlled trial of adrenaline followed by polidocanol has shown a significant reduction in the need for emergency surgery in the treated group[11] In a recent three-way study, Rutgeerts and others compared adrenaline alone with adrenaline followed by polidocanol, and adrenaline followed by laser therapy[12]. They found adrenaline with polidocanol to be superior to either of the other treatments in terms of rebleeding, although there was no significant difference in the eventual need for surgery

Our experience indicates that adrenaline is effective as the sole injectable agent in the treatment of active non-variceal bleeding. It is possible, however, that permanent haemostasis rates could be improved by the addition of a further agent, and the role of adrenaline in the 'prophylactic' management of non-bleeding vessels has not been established. Future research must attempt to identify the most appropriate means of treating individual lesions, and to improve prediction of rebleeding after treatment.

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Selective uptake of glutamine in the gastrointestinal tract: confirmation in a human study

Recent animal data suggest that the gut plays a far more important metabolic role than previously thought. During critical illness, disruption in bowel barrier function may result in a chronic hypermetabolic state and contribute to multiorgan failure. Animal studies have demonstrated that enterocytes of the gastrointestinal tract use glutamine as a respiratory fuel and during critical illness the consumption of glutamine by the gut significantly increases. The selective uptake of glutamine by the gut, to date, has not been confirmed in humans. Seven patients who sustained multisystem trauma necessitating laparotomy underwent portal venous catheterization. This was done by carefully reopening the obliterated umbilical vein and facilitating access to the left branch of the portal vein using a standard central venous catheter. Portal venous and systemic blood samples were recorded for 5 days after operation. Amino acid levels in both circulations were recorded at 48 h and 5 days. Using Student's t *test for related samples, the differences between individual amino acids in portal and systemic circulations were compared. At 48 h, mean(s.d.) portal venous glutamine was 85(5) per cent of the systemic levels (253(80) compared with 296(90) μmol/ml,* $P<0\cdot002$*). At 5 days, portal glutamine was 87(3) per cent of the systemic levels (255(69) compared with 292(83) μmol/ml,* $P<0\cdot003$*). Levels of citrulline, a breakdown product of glutamine metabolism, were elevated in the portal venous circulation at 48 h (20(4) compared with 16(3) μmol/ml,* $P<0\cdot005$*) and at 5 days (21(5) compared with 14(3) μmol/ml,* $P<0\cdot002$*). No significant differences between any of the other amino acids analysed were identified. This study confirms, for the first time in humans, that selective uptake of glutamine occurs in the gut. In stressed states, glutamine deficiency is associated with gut mucosal atrophy. This has significant implications as glutamine is not provided in most commercially available parenteral and enteral nutrition formulations.*

O. J. Mc Anena,
F. A. Moore,
E. E. Moore,
T. N. Jones and
P. Parsons*

*Departments of *Medicine and Surgery, Denver General Hospital and the University of Colorado Health Sciences Center, Denver, Colorado, USA*
Correspondence to:
Mr O. J Mc Anena, Department of Surgery, Mater Misericordiae Hospital, Eccles Street, Dublin 7, Ireland

Following major abdominal surgery or in the immediate period after injury the gastrointestinal tract has been traditionally viewed as an organ of quiescence[1]. Recent animal data have demonstrated that the gut mucosal cells play an important role in amino acid metabolism in both normal and perturbed states[2,3]. In addition, the normal intestine protects the host from intraluminal bacteria and their toxins. After a critical illness there is substantial disruption of the barrier function of the gut, which may result in the egress of enteric bacteria or their toxins, or both.

Glutamine is the preferred fuel utilized for oxidative metabolism by the enterocyte. This has been confirmed in a number of animal studies[1–3]. To date the selective metabolism of glutamine by the gut has not been confirmed in man. In this study, portal venous catheterization via the umbilical vein in trauma patients undergoing laparotomy facilitated the simultaneous measurement of amino acids in the portal venous and systemic circulations to determine whether glutamine was selectively utilized by the gut.

Patients and methods

Seven patients admitted to the Denver General Hospital with major trauma requiring emergency laparotomy were entered into the study. Written consent was obtained from the patient or a near relative. The study was approved by the institutional review body. Following repair of the specific intra-abdominal injury, the occluded umbilical vein was isolated Using Bakes dilators of increasing diameter the lumen was reopened, as described previously[4]. Briefly, the dilators were advanced gently through the reopened umbilical vein until blood spontaneously flowed from the left branch of the portal vein. A size 16 Fr central venous catheter (Deseret®, Tucson, Arizona, USA), primed with heparinized saline was passed into the lumen of the umbilical vein until satisfactory backflow of blood was achieved Having secured the catheter in the umbilical vein with a ligature the catheter passed out of the abdominal cavity via the midline wound and was sutured to the skin. A three-way stopcock was attached; the catheter was primed and patency established by infusion of 30 ml per h heparinized saline (500 units per 500 ml saline) Blood samples were drawn using an aseptic technique. Simultaneous blood cultures were obtained at the time of sampling. Systemic samples were taken from an arterial line. Portal vena cavography was performed on all patients before removal of the catheter on day 5. Amino acid levels in portal and systemic blood were analysed at 48 h and 5 days following catheter placement using a Beckman® (Los Angeles, California, USA) 201M automated amino acid analyser and recorded in μmol amino acid per ml plasma The percentage extraction of individual amino acids was calculated using the formula[5]:

$$\text{Extraction} = \frac{\text{Arterial amino acid} - \text{Portal venous amino acid}}{\text{Arterial amino acid}}$$

All patients required intensive care for the duration of study. Injury

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severity was quantified using the abdominal trauma index[6], injury severity score, revised trauma score and the APACHE II scoring index As part of another study, patients were randomized to placement of a needle catheter jejunostomy or central venous line for enteral or parenteral nutrition, respectively.

Statistical analysis was performed using the Student's *t* test for related samples using PC Statistician® (Human Systems Dynamics, Northridge, California, USA).

Results

Patient characteristics are presented in *Table 1*. Six men and one woman (mean age 31(9) years) were entered into the study. No immediate or delayed complications from umbilical catheter placement were experienced. Nutrition was administered enterally as Vivonex TEN® (Norwich Eaton, Norwich, New York, USA) in five patients and parenterally in two. The mean(s.d.) caloric intake among patients receiving enteral nutrition was 256(20) kCal at 48 h and 1875(85) kCal at 5 days, mean(s d.) nitrogen intake was 1·9(2) g nitrogen at 48 h and 12·6(1·4) g at 5 days. The mean caloric intake for the patients on parenteral nutrition was 812(190) kCal at 48 h and 2132(205) kCal at 5 days; mean(s.d.) nitrogen intake was 5·5(2·9) g at 48 h and 12·0(2·3) g at 5 days

Tables 2 and *3* show the levels of amino acids recorded. At 48 h, portal venous glutamine levels were significantly less than systemic (296(90) compared with 253(80) μmol/ml, $P<0·003$) and remained below systemic levels at 5 days (292(83) compared with 255(69) μmol/ml, $P<0·003$) Glutamine extraction at 48 h was 16(5) per cent at 48 h (*Figure 1*) and 13(3) per cent at 5 days (*Figure 2*) Plasma citrulline levels were significantly increased in portal (20(4) μmol/ml) compared with systemic levels at 48 h (16(3) μmol/ml, $P<0·005$) and at 5 days (21(5) portal compared with 14(3) μmol/ml systemic, $P<0·002$) There were no significant differences between portal and systemic levels of any other amino acids measured. The route of nutritional supplementation did not alter the differences between amino acid levels in portal and systemic circulations in this study .

Table 1 *Characteristics of trauma patients enrolled in the study*

		Trauma patients enrolled in study	
Sex	Age (years)	Injury severity score	Specific injury
M	22	26	Ruptured iliac artery, ruptured jejunum
M	32	32	GSW R chest, lung, diaphgram, liver, duodenum, pancreas
M	37	16	GSW abdomen (high velocity), L colon, renal trauma
M	25	35	Pelvis, open femur and tibia fractures, bladder extravasation
M	18	33	Head injury, fracture both femurs, both tibiae, splenorrhaphy
M	46	34	Head injury, pulmonary contusion, extremity fractures, BKA at accident site
F	28	36	GSW abdomen, splenectomy, distal pancreatectomy, diaphragm repair, colon repair

BKA, below knee amputation; GSW, gunshot wound

Table 2 *Levels of individual amino acids in portal and systemic circulations at 48 h*

	Circulation		
Amino acid	Systemic (μmol/ml plasma)	Portal (μmol/ml plasma)	P*
Alanine	215(28)	225(38)	n s.
Aspartate	11(2)	11(2)	n s
Citrulline	16(3)	20(4)	<0·005
Glutamate	33(13)	29(13)	n s.
Glutamine	296(90)	253(80)	<0·003
Glycine	155(37)	159(31)	n s.
Isoleucine	57(22)	59(8)	n s.
Leucine	143(38)	144(36)	n s.
Methionine	30(7)	31(8)	n s.
Phenylalanine	88(13)	88(13)	n s.
Serine	71(6)	68(11)	n s.
Taurine	35(13)	36(12)	n s
Threonine	90(26)	91(24)	n.s
Tyrosine	45(14)	44(14)	n s
Valine	222(76)	210(65)	n s

n s , not significant, * P, value obtained using Student's t test for related samples. Values are mean(s d)

Table 3 *Levels of individual amino acids in portal and systemic circulations at 5 days*

	Circulation		
Amino acid	Systemic (μmol/ml plasma)	Portal (μmol/ml plasma)	P*
Alanine (ALA)	275(78)	268(39)	n s
Aspartate (ASP)	15(4)	17(4)	n s
Citrulline (CIT)	14(3)	21(5)	<0·002
Glutamate (GLU)	40(10)	41(10)	n s
Glutamine (GLN)	292(83)	255(69)	<0·003
Glycine (GLY)	207(94)	205(85)	n s
Isoleucine (ILEU)	80(50)	71(18)	n s
Leucine (LEU)	180(98)	173(38)	n.s
Methionine (MET)	39(17)	37(5)	n s
Phenylalanine (PHE)	98(20)	98(9)	n s
Serine (SER)	90(31)	81(18)	n s
Taurine (TAU)	35(13)	36(12)	n s.
Threonine (THR)	140(54)	137(52)	n.s
Tyrosine (TYR)	41(8)	44(8)	n s
Valine (VAL)	280(44)	247(107)	n s

n.s., not significant, * P value obtained using Student's t test for related samples. Values are mean(s d)

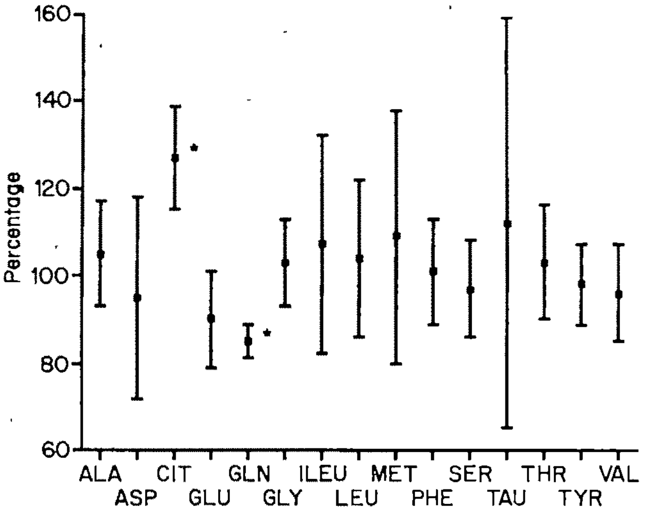

Figure 1 *Percentage extraction of individual amino acids from the systemic circulation at 48 h* * $P<0·05$ *(Student's test for related samples) Values are mean(s d)*

Discussion

Previous investigations of the 'splanchnic bed' which studied the gut and liver as a single unit led to the erroneous conclusion that most of the metabolic activity occurred in the liver[7] Access to the portal venous circulation for a 5-day period using an umbilical vein catheter in this study facilitated partitioning of the splanchnic circulation from the liver and simultaneous

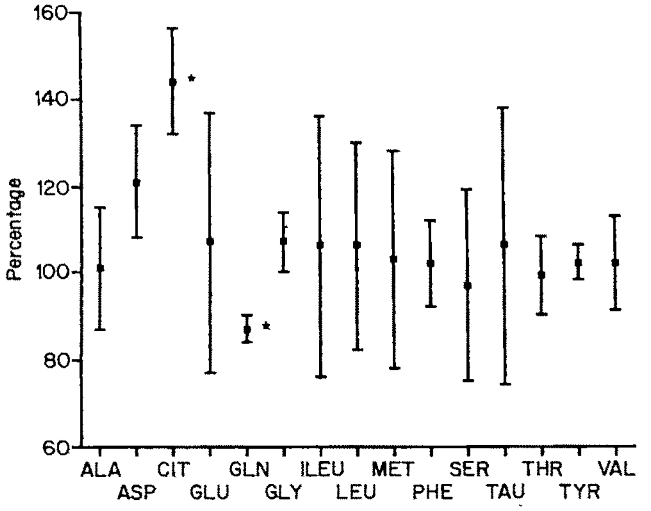

Figure 2 *Percentage extraction of individual amino acids from the systemic circulation at 5 days* *P<0·05 (*Student's* t *test for related samples*). *Values are mean(s.d.)*

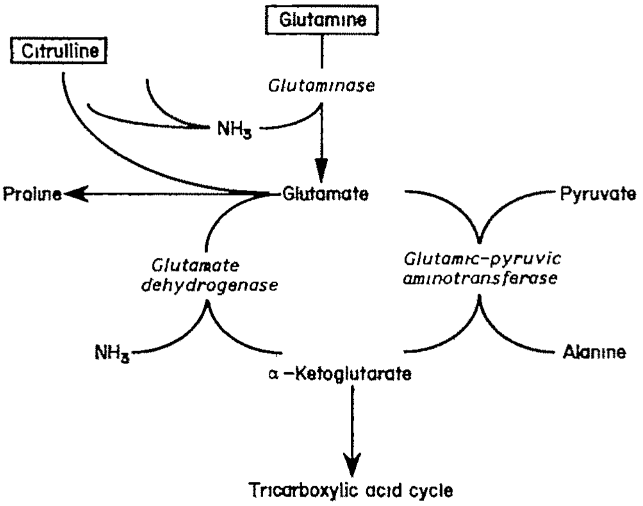

Figure 3 *Pathways of glutamine metabolism in the enterocyte*

measurement of amino acid levels in portal and systemic circulations. In many species, circulating glutamine is removed by the gut and serves as a principal respiratory fuel. *In vivo* and *in vitro* studies demonstrated that the vast majority of this extraction is done by the enterocytes of the small intestine which, despite a high extraction ratio and large glutamine consumption, maintain relatively low levels of intracellular glutamine. This is explained by the presence in the enterocyte of a highly active glutaminase enzyme which rapidly metabolizes glutamine to glutamate and ammonia. Animal studies using the isolated, perfused rat gut preparation and radiolabelled glutamine[2] confirm extensive glutamine oxidation to carbon dioxide, lactate, citrate and citrulline (*Figure 3*). This study demonstrated a significant reduction in portal glutamine levels at 48 h and 5 days in human subjects undergoing surgery following multiple trauma. Portal citrulline levels were elevated at 48 h and 5 days, which is consistent with glutamine oxidation by enterocytes. These findings support previous animal data that the gut is a metabolically active organ following trauma.

The mean extraction of glutamine was 15 per cent at the time points measured. Windmueller has shown that the small intestine of the rat extracts 20–30 per cent of plasma glutamine with each extraction[2]. The net utilization data obtained from arteriovenous difference measurements of glutamine in this study are not quantitative because blood flow rate was not studied.

The wide variation in levels of other amino acids in patients who have sustained severe trauma is consistent with other studies. Vente *et al.*[8] concluded that sepsis and metabolic stress are associated with changes in amino acid profiles, but such changes are non-specific and poor indicators of disease severity.

Citrulline appears to be a significant product of glutamine metabolism by the enterocyte The utility for this pathway is not clear. Citrulline is a precursor for purine and pyrimidine synthesis; the essential building blocks for DNA and RNA synthesis. Using a cardiogenic shock/resuscitation animal model Buchman *et al.*[9] demonstrated an increased expression of specific mRNA and DNA in the pig hepatocyte *in vivo* The availability of DNA and RNA precursors in the portal circulation such as citrulline may therefore be a useful end-product of glutamine metabolism.

This study provides evidence for the selective uptake and metabolism of glutamine following major trauma. In the past, the gastrointestinal tract in these patients would have been considered metabolically inactive. It is probable that the observation reported here in trauma patients also occurs in normal human subjects.

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Stimulation of protein synthesis in human tumours by parenteral nutrition: evidence for modulation of tumour growth

S. D. Heys*†, K. G. M. Park*†, M. A. McNurlan*, E. Milne*, O. Eremin†, J. Wernerman‡, R. A. Keenan† and P. J. Garlick*

**Rowett Research Institute, Bucksburn, Aberdeen, †Department of Surgery, University of Aberdeen, UK and ‡Huddinge University Hospital, Karolinska Institute, Stockholm, Sweden*

Correspondence to:
Mr S. D. Heys, Department of Surgery, University Medical Buildings, Foresterhill, Aberdeen AB9 2ZD, UK

Eighteen patients with localized colorectal carcinoma were randomized to receive intravenous nutrition or to be fasted during the 24 h before surgery. Protein synthesis, an index of tumour growth, was then measured by the incorporation of [^{13}C]leucine into tumour protein immediately before surgery. The mean(s.e.m.) rate of tumour protein synthesis in patients receiving nutrition (42·7(3·5) per cent per day) was 89 per cent higher than the rate in the fasted group (22·6(1·9) per cent per day) (P = 0·002). As tumours consist of a variety of different cell types, in vitro *rates of protein synthesis were measured in malignant cells isolated from colorectal tumours and cultured with autologous serum obtained from the patient in either the fasted or the fed state. There was a mean increase of 81 per cent in protein synthesis when fed rather than fasted serum was used (P < 0·02), indicating that the malignant cells themselves respond to nutrient supply. This increase in tumour protein synthesis provides the first evidence* in vivo *that the exogenous supply of nutrients can modulate the rate of growth of a human tumour.*

Nutritional support has been provided to patients with cancer in an attempt to improve nutritional status, but an unsubstantiated concern has been whether stimulation of tumour growth occurs. Studies in experimental animals have addressed this question by assessing the effects of nutrition on tumour volume, weight, mitotic activity and protein synthesis, using these variables as indices of growth. Conflicting results have arisen, with a stimulation of tumour growth[1–3] or no effect[4–6] being reported. These studies, however, used rapidly growing transplanted tumours or induced tumours, which constitute a large mass relative to the host animal and may not represent the human situation. Studies to date have failed to detect a stimulation of tumour growth in patients given nutritional support[7–10], but reliable clinical assessment of tumour growth rate in humans is difficult and alternative strategies, such as measurement of tumour protein synthesis[10], need to be used.

Measurement of protein synthesis in human tumour tissue has previously been carried out using constant infusions of stable isotopes and radioisotopes[10,11]. Calculation of rates of protein synthesis using this method may lead to errors because of the inability to measure the enrichment of the amino acid at the site of protein synthesis[12]. An approach widely used to overcome this problem in experimental animals and in cell cultures has been to use the 'flooding dose' technique, where a large amount of unlabelled amino acid is given with the isotope as a bolus injection[13–16]. All amino acid pools are rapidly equilibrated to similar isotopic enrichments, thus reducing this potential source of error in precursor pool measurement. We first described this technique to measure protein synthesis in muscle[17] and colorectal tumour tissue[18]. This has enabled the derivation of an index of tumour growth rate and an assessment of the effect of nutrient intake *in vivo* on tumour growth in patients with localized colorectal carcinoma.

Metabolic studies on tumours *in vivo* represent a summation of effects on a number of different cell types which make up the tumour. To determine the specific effects of nutrition on cancer cells we have performed a parallel study in which tumour cells were isolated from colorectal cancers and rates of protein synthesis were measured *in vitro*.

Patients and methods

Patients

All patients were admitted to the Grampian group of hospitals for the investigation and treatment of colorectal carcinoma. They all had localized carcinoma of the rectum with no evidence of metastases at the time of study, and were randomly allocated to either the 'fasted' or the 'fed' group. The study was approved by the Joint Ethical Committee of the University of Aberdeen and the Grampian Health Board, with all patients giving informed written consent.

Protocol

A low-residue diet was given to all patients on days 3 and 2 before surgery, together with Picolax® (Nordic Pharmaceuticals Ltd., Feltham, UK) as a bowel preparation. On the day preceding surgery all oral intake of nutrients was discontinued in both groups. The fasted group was maintained on fluids only, while the fed group was given intravenous nutrition for 20 h. This consisted of amino acids, equivalent to 1·25 g/kg body-weight of protein (Vamin® 9-glucose, Kabi, Bourne End, UK), and energy, 25 kcal/kg body-weight, given as 40 per cent dextrose and the remainder as lipid (Intralipid®, Kabi), together with appropriate supplements of vitamins and electrolytes. Measurements of tumour protein synthesis were made at the end of this period immediately before surgery.

Measurement of protein synthesis rate in vivo

Measurement of protein synthesis was carried out by injecting a bolus of L-[1-^{13}C]leucine (4 g/70 kg body-weight, 19·4 atom per cent in 200 ml of 0·9 per cent saline, intravenously over 10 min during the period just before surgery[17]. At 60–90 min after injection of isotope, anaesthesia was induced. A 100–200 mg biopsy of tumour was taken endoscopically, immediately after induction of anaesthesia, and frozen in liquid nitrogen.

To confirm that the free leucine enrichment in the tumour was similar to that in plasma over the whole time-course of the experiment, four fasted patients were injected with leucine after induction of anaesthesia and a tumour biopsy was taken after 10 min, i.e. at the termination of the injection. An additional three fasted patients were

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injected with labelled leucine after anaesthesia had been induced, and a tumour tissue biopsy was taken after 30 min

Sample preparation

Preparation of tumour biopsies was carried out as described previously, and ^{13}C enrichments of free plasma leucine and tumour tissue protein-bound leucine were determined by isotope ratio and gas chromatography mass spectrometry[17].

Calculations

Fractional rates of protein synthesis in tumours, expressed as the percentage of protein synthesized per day (k_s, per cent/day), were calculated from the following formula[15]

$$k_s = (P_{(t)} - P_{(0)}) \times 100/A$$

where $P_{(t)}$ is the enrichment of protein-bound leucine in the tumour biopsy, $P_{(0)}$ is the natural enrichment of leucine, which was obtained by measurement of plasma proteins isolated from the zero time blood sample of each patient[19], and A is the area under the curve for plasma free leucine enrichment *versus* time (*Figure 1*)

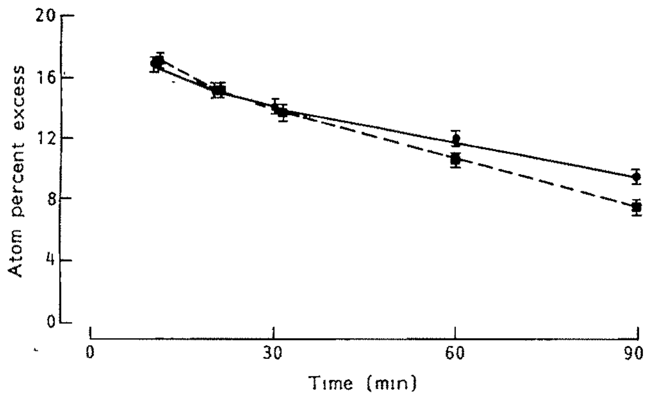

Figure 1 *Plasma leucine ^{13}C enrichments following the administration of labelled leucine ●, Fasted, ■, fed*

The rate of protein synthesis per unit of RNA (k_{RNA}) was calculated from the formula[20]:

$$k_{RNA} = k_s/(\text{RNA/protein})$$

The RNA and protein contents of the tumour were measured as described previously[15]

Measurement of protein synthesis in vitro

A further six patients with localized colorectal carcinomas were given the same intravenous nutritional regimen for 20 h before surgery After surgical removal of the tumour, malignant colorectal cancer cells were isolated as previously described[21] After 7 days of culture in complete medium (RPMI + 20 per cent fetal calf serum), the fetal calf serum was replaced by serum from the patient's own blood. This was taken either immediately before intravenous feeding (i.e. after an overnight fast) or after 20 h of intravenous nutrition After a further 12 h incubation of the malignant cells *in vitro*, protein synthesis rates were measured by the incorporation of [^{3}H]phenylalanine into cellular protein, as described previously[22]

Statistics

Results are expressed as mean(s.e.m.) The statistical significance between means was assessed by Student's t test for the *in vivo* study and by paired t test on log-transformed data for the *in vitro* study

Results

Clinical deails of the patients in whom tumour protein synthesis was measured are listed in *Tables 1* and *2*. There were no significant differences between the nutritional state of the two groups as assessed by body mass index and serum concentrations of albumin and retinol binding protein.

The time course of the enrichments of free leucine (mean(s.e.m.)) in the plasma of the 18 patients in whom tumour protein synthesis was measured showed maximum levels of enrichment immediately after the leucine infusion had finished, followed by a linear fall in each subject (*Figure 1*). The free leucine enrichment in the tumour biopsies, which were taken from each patient between 45 and 90 min after the start of

Table 1 *Clinical details of fasted patients*

Patient	Age (years)	Dukes' classification	Histological differentiation	Serum albumin (g/l)	Retinol binding protein (g/l)	Body mass index (kg/m²)	Weight loss (kg/6 months)
1	80	B	Moderate	40	0·06	21	–
2	60	B	Moderate	42	0·03	23	3
3	74	B	Moderate	40	0·06	21	–
4	76	C	Moderate	36	0·04	24	–
5	73	B	Moderate	39	0·06	18	8
6	62	C	Well	40	0·09	21	–
7	68	B	Moderate	43	0·07	21	–
8	73	C	Poor	36	0·06	18	–
9	77	C	Moderate	34	0·09	22	–

Table 2 *Clinical details of patients receiving intravenous nutrition*

Patient	Age (years)	Dukes' classification	Histological differentiation	Serum albumin (g/l)	Retinol binding protein (g/l)	Body mass index (kg/m²)	Weight loss (kg/6 months)
10	68	C	Moderate	33	0·06	21	–
11	71	C	Moderate	44	0·06	25	–
12	70	C	Moderate	46	0·05	24	–
13	74	C	Moderate	30	0·09	24	–
14	74	C	Moderate	38	0·07	21	–
15	80	C	Moderate	42	0·05	19	7
16	72	C	Moderate	29	0·05	21	–
17	67	A	Well	40	0·06	21	–
18	74	C	Poor	40	0·05	22	–

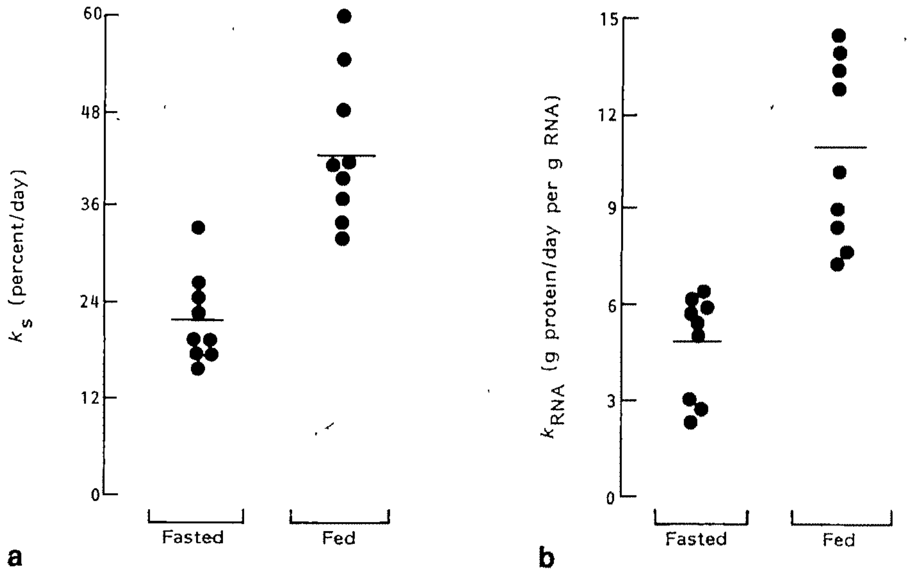

Figure 2 In vivo *rates of protein synthesis in colorectal tumours of fasted and parenterally fed patients* **a** *fractional rates of protein synthesis expressed as percentage of the protein pool synthesized per day* (k_s), **b** *rates of protein synthesis per unit of RNA* (k_{RNA})

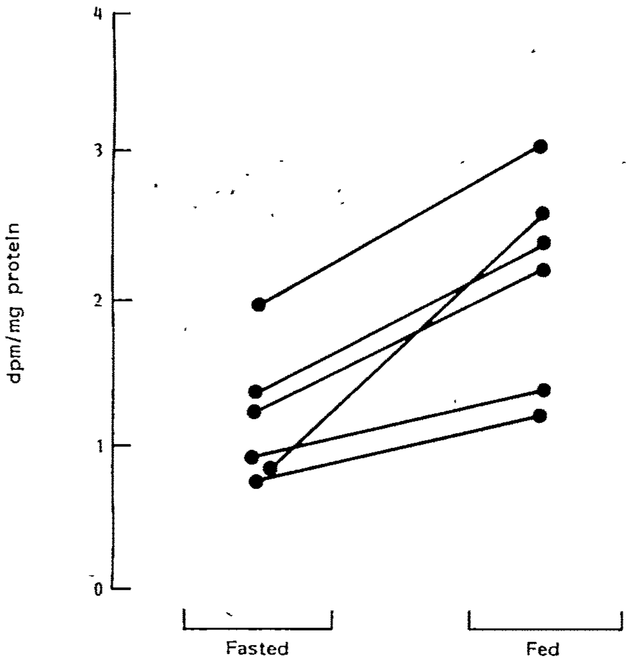

Figure 3 *Rates of protein synthesis* in vitro *in colorectal tumour cells incubated with autologous serum from the patient taken either when fasting or after 24 h of parenteral nutrition. dpm, disintegrations per min*

injection, was compared with that of plasma at the same time. The ratio of tumour to plasma leucine enrichment was 0·90(0·02) in the fasted group and 0·82(0·01) in the fed group (mean(s.e.m)). The enrichment of free leucine in the tumour and plasma at two earlier time points after administration of isotope to a separate group of patients demonstrated that the enrichment in the tumour was 0·97(0·03) ($n=4$) of the corresponding plasma value of 10 min and 0·93(0·03) ($n=3$) 30 min after the start of the injection. Thus flooding, i.e. different amino acid pools reaching similar enrichments, had occurred.

The provision of intravenous nutrition resulted in a significant stimulation of protein synthesis *in vivo* (*Figure 2a*), from 22·6(1·9) per cent per day (mean(s.e.m)) in the fasted state to 42·7(3 5) per cent per day in the fed group ($P=0·002$). The rate of synthesis expressed per g RNA (k_{RNA}) was also significantly increased, from 4·8(0·6) in the fasted group to 10·9(1·0) g protein/day per g RNA in the group receiving intravenous nutrition (*Figure 2b*). The RNA concentration in the tumours was not, however, significantly altered by feeding (data not shown) Therefore, if the total RNA can be taken as indicative of ribosomal content of the tissue[20], the increase in protein synthesis resulted from a change in the activity of ribosomes rather than an alteration in the total number of ribosomes.

The measurements documented above were on total tumour protein, but tumours are well recognized for the heterogeneity of their different constituent cell types[23]. To confirm that malignant cells respond to nutrient intake, colonic carcinoma cells isolated from resected tumours were studied *in vitro* The results are shown in *Figure 3* and demonstrate a significant increase in incorporation of labelled phenylalanine into protein when cells from the tumours of fed patients were incubated with the patient's own fasting serum compared with 'fed' serum ($P<0·02$)

Discussion

This study has demonstrated that protein synthesis in colorectal tumours was substantially higher in patients receiving parenteral nutrition compared with those who were fasted This provides evidence that human tumour growth is susceptible to modulation by nutrient intake In the present investigation the effect of short-term intravenous feeding (20 h) was studied in patients who were nil by mouth for the day preceding surgery There had been no other dietary restrictions except the provision of a low-residue diet to both groups for 48 h. The groups were matched for nutritional state and weight loss. Several previous studies have attempted to assess the effects of long-term nutritional supplementation in humans, but have failed to detect any effect on clinical or biochemical markers of increased tumour growth[7–9].

Determination of the rate of protein synthesis provides an alternative measure of tumour growth and has been used as an *in vivo* index in experimental animals[6]. It has been demonstrated previously that, in human malignant and transformed cells in culture, growth of protein mass is effected by an increase in protein synthesis alone, or an increase in synthesis together with either a decrease or an increase in protein degradation[22,24,25]. Protein synthesis is therefore the primary determinant of growth. Unfortunately measurement of tumour protein breakdown *in vivo* in humans remains impossible. In the present study, breakdown must have been increased, because the increase in tumour growth must have been small in relation to the 20 per cent per day increase in protein synthesis. The average doubling time of human solid tumours has been estimated to be approximately 60 days, which is equivalent to a fractional growth rate of only approximately 1 per cent per day[26].

Measurement of the rate of protein synthesis in human tumours *in situ* by reliable and practical methods has not previously been possible. The present technique for measuring protein synthesis, using a stable isotopically labelled amino acid given as a large or flooding dose, minimizes the errors resulting from precursor compartmentation encountered with other techniques[13,17,18,27]. The single-dose procedure is more readily performed during the hour preceding surgery than the lengthy intravenous infusions used previously[10,11]. Several studies suggest that leucine might stimulate protein synthesis in isolated muscle of growing animals, but there is no evidence that the large dose of leucine injected *in vivo* used in this study might alter protein synthesis in either muscle[17] or tumour[28].

The *in vitro* study demonstrating that serum taken from patients in the fed state stimulated tumour cell protein synthesis confirmed that the malignant cells are able to respond to nutrient intake. These results contradict the concept of the tumour as a growing parasite feeding off the host tissues regardless of the exogenous supply of nutrients. Indeed, it was recently stated that 'malignant tissue is synthesizing protein at a maximal rate and that its rate of growth cannot be affected by the provision of extra nutrients'[29]. This statement was based on the study of Mullen *et al.*[10], who reported that tumour protein synthesis was not significantly different in patients who either ate normally or were given intravenous supplementation, but the experimental groups were not matched and contained different spectra of malignant tumours. Emery *et al.*[6] reported no effect of supplementary feeding on colorectal tumour protein synthesis in rats, but the relevance to humans of this finding is unclear.

The measurements carried out on tumour cells in culture showed that the mediators of this substantial and rapid increase in tumour protein synthesis are present in the plasma from fed patients, but their nature is not clear. In normal tissues, the main mediators of the response of protein synthesis to food intake are insulin and amino acids[30], and insulin is known to stimulate growth of experimental tumours[31]. A number of other growth factors (e.g. epidermal growth factor[28]) have been shown to stimulate the growth of tumour cell lines, and further studies are needed to elucidate the various possible autocrine–paracrine mechanisms responsible for stimulation.

Although nutritional support is frequently provided to patients with malignancy to reverse weight loss and improve nutritional status, these results suggest that feeding might stimulate tumour growth, which might be detrimental to patient survival. Tumour stimulation by nutrient intake may be used to advantage, as experimental animal studies have shown that intravenous nutrition increases the sensitivity of experimental tumours to chemotherapy[32,33] This study using stable isotopes to measure protein synthesis *in vivo* offers an opportunity to investigate the various factors that modulate growth of human tumours.

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Necrotizing fasciitis: 10 years' experience in a district general hospital

R. G. Ward and M. S. Walsh*

Department of General Surgery, Whipps Cross Hospital, London E11 1NR, UK
Correspondence to:
Mr R G. Ward, Senior Registrar, Royal Liverpool Hospital, Liverpool L7 8XP, UK

Of 14 patients with necrotizing fasciitis who presented between 1979 and 1988, six (43 per cent) died. The deaths were associated with delays in diagnosis, poor surgical technique and diabetes. Prompt diagnosis, resuscitation and early radical surgery are essential to the successful management of necrotizing fasciitis.

Necrotizing fasciitis is a pathologically descriptive name applied to a life-threatening infection, characterized by rapidly developing gangrene of the subcutaneous tissue with subsequent death of the overlying skin[1] It is an uncommon condition with a high mortality rate[2]. A retrospective survey of the condition has been undertaken to determine which factors affect outcome and to develop a management plan.

Patients and methods

A retrospective review of the records at Whipps Cross Hospital covering the 10 years from 1979 to 1988 identified all patients with serious soft tissue infection The notes of patients with necrotizing fasciitis were analysed with respect to presentation, management and outcome. Clostridial gas gangrene, Fournier's gangrene and other soft tissue infections were excluded.

Results

Fourteen patients who had necrotizing fasciitis were identified of whom six died, giving a mortality of 43 per cent The mean age of the patients was 59 years (range 25–79 years). The eight survivors had a mean age of 57 years and the six non-survivors of 60 years.

The patients presented to a variety of specialist teams including accident and emergency, gynaecology, urology, orthopaedics, general medicine, care of the elderly, and general surgery. One of the six non-survivors was seen by a general surgeon within 24 h of admission compared with six of the eight survivors The mean time to diagnosis was 1·5 days (range 0–4) for survivors and 6 days (range 1–18) for non-survivors.

The management and outcome of patients with necrotizing fasciitis are shown in *Table 1*. It can be seen that the site affected did not influence the outcome. The disease occurred secondary to bowel perforation in cases 4, 7, 9 and 14, following ischiorectal sepsis in cases 5 and 11, following labial abscesses in cases 2 and 13, as a consequence of trauma in case 1, and as a consequence of diabetic leg ulcer in case 12. Two patients developed necrotizing fasciitis secondary to renal calculi (cases 6 and 8), an association which has not previously been reported. Two patients (cases 3 and 10) had no apparent underlying lesion. There was no demonstrable association between aetiology and mortality.

The clinical features of necrotizing fasciitis were similar in all patients. In the early stages clinical signs were minimal, with pain disproportionate to these signs Disease progression was marked by development of swelling and dusky cellulitis leading to skin blistering, necrosis and crepitus. The rate of progression was unpredictable, varying from hours to several days. Twelve of the 14 patients had systemic features of sepsis.

After diagnosis all patients were managed in the intensive care unit General treatment consisted of aggressive fluid replacement and broad-spectrum antibiotics with inotropic support, ventilation, parenteral nutrition and renal dialysis if indicated.

Necrotizing fasciitis was confirmed at operation in 13 patients by the presence of typical grey necrotic fascia. The extent of the fascial necrosis was invariably more widespread than changes in the overlying skin In one patient (case 10) the diagnosis was made on clinical and microbiological grounds. Active surgical intervention was withheld because of a combination of severe diabetic complications.

Aggressive debridement early in the course of the disease was carried out in seven patients (cases 1–7), all of whom survived. Only one (case 8) of five patients (cases 8, 11–14) operated on late in the course of the disease survived. Several technical failures also deserve comment. An inappropriate initial procedure was performed in two patients (cases 8 and 14). Multiple incisions rather than debridement were carried out in one patient (case 9) who subsequently died. Necrotic tissue was known to have been left behind at the initial operation in two patients (cases 11 and 12), both of whom died.

All four diabetic patients died. There was significant delay in diagnosis in three (cases 9, 12 and 13) with inadequate surgery in two of these patients (cases 9 and 12). In one (case 10) a decision was made not to operate.

The commonest organisms isolated from operative specimens were coliforms (10), *Bacteroides* spp. (7) and *Streptococcus faecalis* (5). No positive preoperative blood cultures were obtained. In all cases at least two organisms were present, most commonly an anaerobe with a facultative aerobe (Giuliano type I)[3]. One patient cultured haemolytic streptococci and *Staphylococcus aureus* (Giuliano type II)[3]. There were no differences in clinical features or outcome attributable to the bacteriological findings.

Discussion

This series demonstrates that delayed diagnosis and inadequate surgery are the most important factors contributing to the mortality of necrotizing fasciitis, confirming previous reports[2,4–11].

The 43 per cent mortality rate is similar to that of a previous UK series[4]. However, prospective studies using historical controls have shown that the mortality rate can be reduced to 10 per cent by aggressive early management[5,12,13]. A 100 per cent mortality rate in diabetics with necrotizing fasciitis has been previously reported but aggressive treatment reduced the mortality to 20 per cent[5]. Only two of the present seven patients over the age of 60 years died, although old age has been associated with high mortality rates[10]. The presence of diabetes or the age of the patient should not, therefore, influence the decision to offer active management. Site or aetiology of necrotizing fasciitis did not influence mortality rate here, but a favourable prognosis has been associated with necrotizing fasciitis of the extremities due to trauma or intravenous drug abuse[7,9,12].

Necrotizing fasciitis is uncommon, only 1·4 cases per year

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* *Present address Surgical Unit, The London Hospital, Whitechapel, London E1 1BB, UK*

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Table 1 *Management and outcome of patients with necrotizing fasciitis*

Case	Presenting site	Time to diagnosis	Time to operation	Local treatment	Outcome
1	Both legs, right forearm	At admission	12 h	Wide excision, skin grafts	Survived
2	Right labia, perineum and thigh	72 h	80 h	Wide excision	Survived
3	Right thigh	4 days	4 days	Wide excision, skin grafts	Survived
4	Left thigh	At admission	2 h	Hip disarticulation and wide excision	Survived
5	Perianal	3 h	6 h	Wide excision	Survived
6	Right flank and thigh	4 h	12 h	Wide excision, skin grafts	Survived
7	Left thigh and groin	At admission	6 h	Wide excision, skin grafts	Survived
8	Abdominal wall, right groin and thigh	3 days	6 h 3 days	Perinephric abscess drained Wide excision, skin grafts	Survived
9*	Left thigh	At admission	12 h	Longitudinal incisions	Died
10*	Abdominal wall	At admission		None	Died
11	Perianal and abdominal wall	2 days, at operation	2 days	Incomplete debridement	Died
12*	Left leg, thigh, buttock and flank	3 days	4 days	Above knee amputation, incomplete debridement	Died
13*	Vulva, both thighs and abdominal wall	18 days	19 days	Wide excision	Died
14	Right groin and thigh	30 h	36 h 60 h	Laparotomy Wide excision	Died

* Diabetic

in this series, but may present to any speciality[14–16] with fatalities from apparently trivial initial lesions. Awareness of this condition is important since we have demonstrated that early surgical referral improves subsequent outcome.

The following management plan may be advocated.

1. Early surgical referral of patients with atypical cellulitis, particularly when pain is disproportionate to the area of involvement.
2. Prompt resuscitation with intravenous fluids, broad-spectrum intravenous antibiotics and analgesia, with intensive care involvement.
3. Diagnostic incision[13] of the affected site to inspect the underlying fascia should be performed at the earliest opportunity, with pus sampling for urgent Gram stain and culture.
4. Radical debridement of all the involved tissues should immediately be performed if fascial necrosis has been found. Lesser procedures have been shown here and in other series[4,5,11,12] to result in high mortality rates.
5. Wound inspection under anaesthetic at 24 h to confirm the adequacy of debridement or to complete debridement[6].
6. Once clearance of devitalized tissue has been achieved, reconstructive manoeuvres aimed at skin coverage may be instigated.

This regime is similar to that recently advocated for Fournier's gangrene[17,18] which may be considered as necrotizing fasciitis of the male genitalia. However, while Fournier's gangrene is well recognized, necrotizing fasciitis may be less well known, and lack of awareness among clinical staff may play a major role in the delay of diagnosis with subsequent high mortality.

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Surgical implications of drug-induced rhabdomyolysis

P. H. Rutgers,
E. van der Harst and
R. K. J. Koumans

Department of Surgery, Westeinde Hospital, The Hague, The Netherlands

Correspondence to.
Dr P H. Rutgers, Department of General Surgery, Academic Hospital State University of Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

Four cases are described of acute non-traumatic rhabdomyolysis with subsequent development of a compartmental syndrome, requiring extensive fasciotomies. All the patients were young male alcoholics who were taking benzodiazepines as part of an addiction treatment programme. In this risk group clinicians should be aware of two serious complications of non-traumatic rhabdomyolysis: acute renal failure and compartmental syndrome.

Rhabdomyolysis has been defined as reversible or irreversible injury of skeletal muscle which alters the integrity of the cell membrane sufficiently to allow the escape of cell contents into the extracellular fluid[1]. The syndrome was first described in the German literature in 1881 as 'a new form of haemoglobinuria', referring to myoglobinuria, which is the result of release of myoglobin from the damaged muscle cells into the plasma and subsequently into the urine[2] The traumatic form of rhabdomyolysis, as part of the crush syndrome, was first reported in patients with major trauma during the Battle of Britain[3]. These authors were the first to relate acute renal failure to rhabdomyolysis. In the 1950s and 1960s a series of papers from Scandinavia described a form of non-traumatic rhabdomyolysis as a complication in 'binge' drinking alcoholics[4–6] Since then numerous non-traumatic causes have been reported. Alcohol abuse, compression and generalized seizures are presumed to be the most common aetiologies[1,7].

Although non-traumatic rhabdomyolysis can be extensive, in most reported cases the muscle disease is self-limiting, leading to complete recovery in days or weeks[1,7] Most authors stress the importance of prevention and management of its most serious, sometimes fatal, complication, myoglobinuric acute renal failure (MARF)[7–9]. Much less emphasis, however, has been put on surgical aspects of non-traumatic rhabdomyolysis

We describe four cases of fulminant rhabdomyolysis without preceding trauma or major surgery. The clinical course of these patients was dominated by surgical complications. All patients were relatively young men with a history of alcohol abuse, in two cases combined with heroin abuse. They had all tried to overcome their addiction and received benzodiazepines as a component of treatment programmes provided by specialized centres

Case reports

Case 1

This 35-year-old man was admitted from a nearby institution where he had been voluntarily hospitalized for 3 weeks and treated with calcium carbimidecitrate and chlordiazepoxide (20 mg/day) for chronic alcohol abuse Three days before admission he was allowed to spend the weekend at home In this period he drank excessive amounts of alcohol and swallowed several kinds of benzodiazepine (up to a total of 600 mg oxazepam, 600 mg lorazepam and unknown quantities of diazepam and flunitrazepam) The day before admission he experienced paraesthesia in his knees and ankles, and bilateral weakness in his arms and legs. On admission he complained of severe muscle pains in his legs, buttocks and back. On physical examination, the muscles of both thighs and the right crural musculature were diffusely swollen and extremely tender on palpation He could not move his legs because of severe myalgia on exertion Both ankle jerks were absent Further neurological examination disclosed a slight sensory loss of the distal lower extremities. Urine was brown and contained protein On microscopy of the urinary sediment no red blood cells could be seen The orthotolidine stick test, however, was positive Laboratory data on admission were creatine phosphokinase, 60 000 units/l, blood urea nitrogen (BUN), 23 5 mmol/l; creatinine, 397·0 μmol/l, serum sodium, 126 mmol/l; serum potassium, 5 8 mmol/l Urine toxicology was positive for chlordiazepoxide Ethanol could not be detected Because of progressive muscle swelling, a presumptive diagnosis of a compartmental syndrome, secondary to acute rhabdomyolysis, was made Fasciotomies of all femoral compartments of his left leg, of the left gluteal muscles, and of all crural compartments of his right leg were performed Biopsies of the right tibialis anterior, the left vastus lateralis and the left gluteus maximus showed necrosis of almost every muscle fibre Both types I and II muscle fibres were involved. Three days after operation five sessions of haemodialysis were required for control of uraemic symptoms. Further debridement of necrotic muscle tissue had to be performed three times. After 3 months of hospitalization the fasciotomy wounds were covered with split skin grafts and the patient was referred to a rehabilitation clinic. At this time there was still a complete paralysis of muscles innervated by the right peroneal nerve

Case 2

A 45-year-old chronic alcoholic was sent to our hospital from a psychiatric clinic, where he had been admitted the night before because of a suicide attempt by ingestion of 300 mg nitrazepam On admission he was somnolent and disoriented and complained of generalized muscle pain Myalgia on exertion was so severe that he was not able to move his arms or legs He had been completely anuric for the past 24 h. On examination the muscles of his left calf were swollen and very tender on palpation Peripheral pulsations of both legs were readily palpable. Physical examination revealed no further abnormalities, other than a slight dehydration Laboratory data on admission were creatine phosphokinase, 18 105 units/l, BUN, 16 5 mmol/l, creatinine, 544 μmol/l, serum sodium, 130 mmol/l, serum potassium, 4 7 mmol/l. Urine tests showed evidence of myoglobinuria. Urine toxicology screening was negative for common toxins Ethanol could not be detected

Although ultrasound examination disclosed no abnormalities of the deep venous system, left calf thrombosis was suspected and heparin therapy was started At this time no full evidence of a compartmental syndrome existed The patient was admitted to the department of internal medicine, where dehydration and renal failure were adequately treated. However, despite heparinization, swelling and myalgia of the left calf musculature worsened and rhabdomyolysis, causing a compartmental syndrome, was suspected. On the 12th day of hospitalization fasciotomy of the left posterior crural compartment was performed Histological examination showed haemorrhagic necrosis and evidence of acute inflammation of muscle fibres. After three subsequent necrosectomies on days 6, 10 and 15, the wounds were closed with split skin grafts 1 month after operation. After 4 months of hospitalization the patient was discharged At this time foot-drop of his left leg was still present

Case 3

A 29-year-old man had a 10-year history of alcohol abuse and was addicted to heroin For 1 week before admission he was withdrawn from heroin In order to control the withdrawal symptoms he had been using 30 mg methadone and approximately 150 mg chlordiazepoxide daily The night before admission he suddenly experienced burning sensations in his right arm and paraesthesia in all fingers of his right hand. In addition, swelling of his right arm developed These symptoms intensified during the night and, on arrival at the emergency ward the next morning, active movements of his right arm were impossible On

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physical examination there was a tight tender swelling of the right deltoid and of all the muscles of the right forearm. Radial artery pulsations were normal but there was impairment of cutaneous sensation of the whole right arm, including the deltoid region. Physical examination was otherwise unremarkable.

Biochemical values on admission were: creatine phosphokinase, 3507 units/l, BUN, 8·7 mmol/l; creatinine, 170 μmol/l, serum sodium, 135 mmol/l, serum potassium, 6·9 mmol/l. Urine analysis showed evidence of myoglobinuria Because of oliguria, he was initially admitted to the intensive care unit. The acute renal failure was conservatively treated. The muscle swelling, however, worsened and therefore fasciotomy of the right deltoid and of all muscle compartments of his right forearm was performed Macroscopically these muscles were oedematous and focal necrotic lesions were seen Biopsies of extruded muscle tissue showed focal haemorrhagic necrosis of muscle fibres with inflammatory infiltrations After operation muscle swelling gradually decreased and muscle strength was regained. Three weeks after operation the wounds were covered with split skin grafts and a few days later the patient was referred to a local addiction clinic

Case 4

A 22-year-old man had been using heroin for several years and was a chronic alcoholic. A few days before admission he presented for treatment at an addiction clinic. However, because of matrimonial problems, he tried to commit suicide by ingesting large doses of benzodiazepines According to his friends, he subsequently had been lying on the floor motionless for about 24 h On admission he was totally unresponsive Both pupils were constricted and did not react to light. His blood pressure was too low to be measured. Pulse rate was 45 beats/min Respiration was depressed. Laboratory data were: creatine phosphokinase, 37 900 units/l; BUN, 11 9 mmol/l; creatinine, 335 μmol/l, serum sodium, 141 mmol/l; serum potassium, 8·6 mmol/l Urine tests showed evidence of myoglobinuria Urine toxicology screening was positive for derivatives of heroin, diazepam and nordiazepam. Ethanol could not be detected Soon after admission cardiorespiratory arrest necessitated intensive resuscitation with cardiac massage and artificial ventilation. Adequate cardiac output was restored soon after administering naloxone, adrenaline, isoprenaline and atropine. In the intensive care unit rapid swelling of the left femoral and the left gluteal muscles developed For this reason fasciotomy of these muscle compartments was carried out. The postoperative period was complicated by acute renal failure, which was treated successfully with five sessions of haemodialysis. Muscle function improved gradually and after 6 weeks of hospitalization the patient was discharged in relatively good health

Discussion

The clinical picture of non-traumatic rhabdomyolysis ranges widely from an asymptomatic, transient elevation of the muscle isoenzyme fraction of serum creatine phosphokinase to fulminant necrosis of muscle cells with myoglubinuria[1,7,10]. The classical presentation of the more severe forms of this syndrome is the triad of acute muscle weakness, pain and swelling. Muscle symptoms may either be generalized or may involve discrete muscle groups, particularly the calf musculature[10]. Post-mortem studies of fatal cases following heroin[11] and alcohol[6,12] overdoses have shown that myonecrosis can be widespread with the involvement, among others, of the pharyngeal, sternocleidomastoid and pectoral muscles. Thrombophlebitis, dermatological (e.g. erysipelas), neurological, rheumatic (e.g. polymyositis, polymyalgia rheumatica) and other causes of acute muscle symptoms also have to be considered in the differential diagnosis A difficulty in diagnosing non-traumatic rhabdomyolysis is that patients are commonly disoriented and confused, or even comatose, and therefore not able to complain of muscle pain and weakness. In such patients the condition should be suspected when limbs are swollen and indurated.

Oliguria or even anuria during the first few hours after admission is an alarming symptom. Urine, spontaneously voided or obtained by catheterization, frequently appears to be tea-coloured. The differential diagnosis of this pigmented urine includes myoglobinuria, haemoglobinuria, haematuria, porphyria and bilirubinuria The combination of a positive orthotolidine stick test, no red blood cells in the urine and colourless serum with a normal haptoglobin level confirms myoglobinuria[7]. Serum and urine concentrations of myoglobinuria, however, may have returned to normal by the time of hospitalization, due to the rapid clearance of myoglobin from plasma[1]. The most suggestive laboratory abnormality is a high level of creatine phosphokinase. Other muscle cell constituents that escape in the extracellular volume and cause an elevation of their serum levels are glutamic oxaloacetic transaminase, aldolase, potassium phosphate and purines.

The most frequently reported complication of non-traumatic rhabdomyolysis is MARF[7–9]. Approximately one-third of patients with the condition will develop MARF[1], which is biochemically characterized by a rapidly increasing creatinine concentration (>150 μmol/l in 24 h) and a disproportionally high creatinine:urea ratio. Early in the course of MARF a transient period of hypocalcaemia may develop, followed by hypercalcaemia in the diuretic phase[13].

The pathogenesis of MARF remains uncertain Hypotheses that have been proposed to explain its development include plugging of tubules by myoglobin-containing casts, altered renal haemodynamics with a decreased glomerular filtration rate, direct toxicity of myoglobin in the presence of hypovolaemia or aciduria, direct and indirect toxicity of intramyocellular constituents, and causative factors often associated with non-traumatic rhabdomyolysis, such as intravascular coagulation and hyperthermia[7,14]

A rarely reported complication of non-traumatic rhabdomyolysis is the development of a compartmental syndrome In one study only two of 77 patients required fasciotomy for this reason[1]. A considerable delay between admission, diagnosis and surgical treatment can occur, owing to unfamiliarity with signs and symptoms of a compartmental syndrome, where these patients have been admitted to nephrology units[15]

Much of the pathogenesis of the compartmental syndrome associated with non-traumatic rhabdomyolysis is unknown Usually it is subsequent to prolonged coma and immobility, following overdoses of various drugs The most important pathogenetic factor in these patients seems not to be a specific myotoxic effect of a drug, but the effects of external pressure, induced by the patient's own body-weight[16].

On the other hand, cases of drug-induced non-traumatic rhabdomyolysis have been reported, which were not associated with coma or immobilization. Several reports concerning this direct myotoxic effect have been published in cases of alcohol[10] and heroin[11,17] intoxication. Because intoxications with alcohol[18] and heroin[19] can cause acute myolysis of cardiac muscle as well, direct toxicity is very likely to be of aetiological importance.

In this series, coma on admission was present only in case 4. In this patient, compression by prolonged immobilization was probably the most important myonecrotic factor It is remarkable that all four patients consumed high doses of benzodiazepines In the medical literature we have found only one case report in which a possible role of benzodiazepines in the aetiology of non-traumatic rhabdomyolysis was presumed In this case acute rhabdomyolysis developed following an overdose of 250 mg nitrazepam and 1250 mg doxepin[20]. This patient had not been immobilized and was not comatose, so the authors concluded that the condition was probably caused by nitrazepam, doxepin or a combined effect of the two drugs. All our patients were heavy drinkers and two of them had been using heroin More than one aetiological factor can be identified in all four cases. This is in agreement with the literature, where multiple factors, capable of injuring muscles, were found in 59 per cent of cases[1].

The treatment of choice in compartmental syndrome, regardless of aetiology, is urgent fasciotomy When surgical intervention is delayed, muscle cell necrosis will further increase interstitial pressure and vice versa, leading to a viscious circle. Nerves are damaged by external pressure, ischaemia and intracompartmental pressure[16] The pre-existing polyneuropathy in chronic alcohol abuse makes neurons even more sensitive to intracompartmental pressure. Debridement of potentially viable muscle and nerve should be kept at an absolute minimum at the time of surgical decompression, because these tissues have the potential to recover after an ischaemia insult. Tissue pressure measurements possibly aid in the decision of whether or not surgical intervention is indicated It has been suggested that fasciotomy should be performed when the tissue pressure within a muscle compartment rises to within 10–30 mmHg of the patient's diastolic blood pressure[21].

In all cases the typical morphological changes of acute rhabdomyolysis, as reported in the literature, were found. Biopsies of involved muscles and histological examination of muscle tissue obtained at surgery showed myofibrillar degeneration and regeneration[7]. Occasional perivascular and interstitial inflammatory infiltrates could be seen. In early stages of alcoholic non-traumatic rhabdomyolysis type I fibres were reported to be predominantly affected, with patchy loss of oxidative enzyme activity in some fibres[22]. In the heroin-associated condition, myolysis of all muscle fibres is seen[11]

We conclude that, in addition to MARF, development of a compartmental syndrome is an important complication in drug-induced non-traumatic rhabdomyolysis, even in the absence of preceding coma or complete immobility for long periods of time. As patients will frequently be intoxicated, this complication can easily be overlooked A causal relationship between ingestion of high doses of benzodiazepines and non-traumatic rhabdomyolysis in alcoholics and drug addicts seems likely, but is hard to prove because of the probable multifactorial aetiology of the syndrome

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Carbon dioxide laser ablation of cutaneous metastases from malignant melanoma

R. A. Waters,
R. M. Clement* and
J. Meirion Thomas

*Westminster and Royal Marsden Hospitals, London, and *West Glamorgan Institute of Higher Education, Swansea, UK*

Correspondence to
Mr J Meirion Thomas,
Department of Surgery,
Westminster Hospital, Dean Ryle
Street, London SW1P 2AP, UK

Multiple cutaneous and superficial subcutaneous metastases from malignant melanoma in 30 patients were treated palliatively by carbon dioxide laser ablation when lesions were too numerous, too large or recurring too rapidly for multiple local excisions. The number of lesions per patient ranged from three to 250 (median 30). Patients were treated under local or general anaesthetic and as day cases or inpatients. After a median follow-up interval of 8 months fewer than 1 per cent of lasered metastases have recurred locally. Sixteen patients have developed cutaneous metastases at other sites requiring further treatment. Approximately 2000 lesions have been treated on 64 occasions. Patients reported little or no pain after the operation and required only simple dry dressings. Wounds were completely healed in 2–6 weeks with good cosmetic results. This simple and effective treatment is becoming an alternative to isolated limb perfusion.

Malignant melanoma has a diverse pattern of metastatic spread by lymphatic and haematogenous routes with an ability to metastasize selectively to skin and subcutaneous tissue in the absence of detectable spread to other sites. Untreated these lesions enlarge, ulcerate, become painful and unsightly and most patients will die from metastatic disease.

Local excision of individual lesions is impractical when they are numerous, large or recurring with a short disease-free interval. Other methods of local ablation such as diathermy or cryosurgery may be used but their efficacy has not been reported. When the lesions are confined to a limb, isolated limb perfusion (ILP) is an important treatment option[1]. Systemic chemotherapy, immunotherapy and local radiotherapy have all demonstrated only limited effectiveness[2].

Because of its wavelength, carbon dioxide (CO_2) laser radiation is highly absorbed by soft tissues and therefore dissipation of heat to surrounding tissues by conduction is reduced, thus minimizing thermal damage[3]. Its role in the treatment of widespread metastases of malignant melanoma has not been reported.

Patients and methods

Thirty patients with cutaneous metastases of melanoma who had lesions which were too numerous, too large or recurring too frequently for local excision were selected for laser treatment. Patients with recurrences following ILP were included as well as those in whom ILP was contraindicated, i.e. patients with visceral metastases or cutaneous lesions not confined to a limb. Seventeen patients would have been suitable for ILP but were selected for laser ablation knowing that ILP would be an option if laser treatment failed to achieve local control. Lesions up to 2 cm in diameter were considered suitable for laser vaporization as were superficial subcutaneous lesions attached to skin. Deep subcutaneous nodules were treated by local excision and primary suture. *Table 1* summarizes the sites of the lesions in the patients.

A Shanning Sirius 300 portable CO_2 laser (Shanning Laser Systems, University Innovation Centre, Swansea, UK) was used. This has an articulated arm for free hand use and was used with a 50 mm lens which, at its focal point, gives a spot size of 0·05 mm. The CO_2 laser beam has a wavelength of 10·6 μm which is in the far infrared range of the spectrum and therefore a visible helium neon aiming beam is incorporated. Local or general anaesthesia was used depending on the number, size and distribution of the lesions to be treated. Many were treated as day cases but elderly patients undergoing general anaesthesia and those travelling from greater distances stayed for one or two nights.

Each lesion was totally destroyed using a fully focused laser beam of spot size 0·05 mm at 10–20 watts (power density 0·5–1·0 megawatts cm^{-2}). The plume was removed by a powerful smoke evacuator. Scalp and face wounds were left exposed but elsewhere dry dressings were applied until a dry eschar had formed.

Results

Laser vaporization was a highly efficient method of ablating cutaneous metastatic melanoma. Patients with 10–20 small lesions were treated under local anaesthetic in less than 15 min and up to 250 lesions were treated in one session. In most cases the tumours involved the full thickness of skin and, therefore, a full thickness skin defect resulted. Some lesions were found to be very superficial and could be separated from the dermis by the laser beam leaving a wound which scabbed and healed rapidly. After the operation pain was absent or minimal. Only one patient experienced delayed wound healing following laser ablation. This was thought to be due to failure of the smoke evacuator during the procedure since efficient smoke evacuation has been found to be important in limiting thermal damage at the wound edge[4].

Fourteen patients required only one laser treatment for control of their cutaneous disease with a median follow-up of 8 months. Of these patients ten would otherwise have been suitable for ILP (although in one patient the procedure was

Table 1 *Sites of lesions treated by laser ablation*

Site	No of patients
Limbs only	
No previous ILP	18 (1)
Following ILP	5 (1)
Following second ILP	1
Limbs and trunk	
No previous ILP	1
Following ILP	3 (2)
Head and neck	1
Head and neck, trunk, limbs, subungual	1

Figures in parentheses indicate patients with visceral metastases at the time of their first laser treatment. ILP, isolated limb perfusion

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contraindicated because she refused blood transfusion). The remaining four patients had already had an ILP previously.

Recurrences at a previously lasered site were rare (<1 per cent) and, although 16 patients later developed cutaneous metastases at new sites, these were easily treated by further laser ablation (the total number of treatments for each patient was: one treatment, 14 patients, two treatments, seven patients; three treatments, four patients; four treatments, two patients; and five, six and seven treatments, one patient each). Analysis of these 16 patients reveals that four of the patients were unsuitable for ILP either because their lesions were not confined to a limb or because they already had visceral metastases Five of the patients had previously had an ILP and seven would otherwise have been suitable for ILP Of the five who had previously had ILP the mean number of laser treatments was 4·6 and for those who would have been suitable for ILP it was 2·7.

Four of the patients selected for laser ablation were known to have visceral metastases at the time of their first laser treatment. Two of these have since died of their disease while the other two are well and free of cutaneous disease. All other patients are currently clinically disease-free.

Discussion

A method has been described for the local ablation of cutaneous metastases of melanoma. In the absence of a cure the aim of treatment is palliation, implying effective control of cutaneous disease with minimal side effects and minimal disruption of the patient's life. This treatment fulfils these criteria.

Good wound healing following treatment depends on using the CO$_2$ laser with a high-power density This allows rapid vaporization of tumour with little time for dissipation of heat to surrounding normal tissue. During the vaporization procedure tumour tissue, particularly when melanotic, can easily be distinguished from normal tissue and selective vaporization is thus possible without removal or damage to surrounding normal tissue. Other methods of local ablation such as diathermy or cryosurgery are less precise and a wider margin of normal tissue is destroyed to ensure tumour necrosis

For the treatment of disease which would otherwise be suitable for ILP, laser ablation should be considered as a realistic first option The morbidity and available results of both treatments require comparison. Laser ablation may be conducted on a day case basis and is a simple procedure allowing the patients to return quickly to their normal daily routine. Local recurrences at previously lasered sites are rare and there is no contraindication to further laser treatment if new lesions appear. No patient in our series has required amputation

In contrast, ILP is a major surgical procedure with significant morbidity[1] and mortality[1,5] rates which lasts approximately 3 h and requires hospitalization for about 25 days[6]. The objective response rate to ILP is reported as 73–91 per cent[5,7,8] but the mean duration of response is 14·9–23·3 months[5,8,9]. Overall figures for relapse after complete response are 30–35 per cent[5,8,10]. Despite an initially good response rate, therefore, ILP offers a limited duration of response and a high relapse rate

The financial saving of treatment by laser is considerable According to the Riverside Health Authority cost returns for 1989/90, the cost of an ILP is about £6500 compared with £680 for day case laser treatment, plus £180 for each overnight stay. The capital cost of the laser (£25 000) is not included.

Having had considerable experience with ILP[5], the limited benefits of this complex technique stimulated the search for an alternative treatment option. These initial results with laser ablation are encouraging Fourteen of 30 patients are disease-free following a single laser treatment after a median interval of 8 months, and ten of these would have been suitable candidates for ILP. Seven patients suitable for ILP have required more than one laser treatment (mean 2·7 treatments) and it could be argued that this sub-group should now be offered ILP.

In conclusion, laser ablation of cutaneous and superficial subcutaneous metastases is a simple and safe treatment for patients with post-ILP recurrences and for patients unsuitable for ILP. Laser ablation should be considered as the initial treatment to assess the duration of response for patients otherwise suitable for ILP.

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Povidone-iodine in experimental peritoneal hydatidosis

Ö. Gökçe, Ç. Gökçe*, M. Yilmaz†, K. Hüseyinoğlu and S. Günel

*Departments of Surgery, *Internal Medicine and †Microbiology, Firat University School of Medicine, Elazığ, Turkey*

Correspondence to:
Dr O. Gokçe, Firat University Hospital (Araştırma Hastanesi),
23200, Elazığ, Turkey

The effect of polyvinylpyrrolidone-iodine (PVP-I) on experimental peritoneal hydatidosis was evaluated in this randomized blind controlled study. Seventy-five white, 3-month-old rats were subjected to laparotomy. After the intraperitoneal inoculation of viable scolices, the rats were randomly divided into three groups. Their peritoneal cavities were irrigated with either 1 per cent PVP-I solution (the PVP-I group), hypertonic saline (the HS group) or Ringer's lactate (the control group). Each group was assigned a separate code number; observers blind to the meaning of the code numbers noted all findings during a period of 4 months, after which the rats were killed to allow assessment of the abdominal cavity. The results were decoded after the statistical analyses were completed. The incidence of peritoneal cysts was found to be lower (8·7 per cent) in the PVP-I group compared with the HS (50 per cent) and control (90·9 per cent) groups; the mean number of hydatid cysts per animal was also lower in the PVP-I group compared with the other two groups. We conclude that the scolicidal activity of PVP-I is significantly higher than that of hypertonic saline and that it can be employed as a prophylactic agent against peritoneal hydatidosis.

Hydatid disease continues to be an important and endemic problem in many parts of the world. Surgical intervention is still the preferred method of treatment but carries the risk of intraoperative spillage of scolices. Furthermore, preoperative spontaneous rupture of, or leakage from, cysts occurs quite frequently. Irrigation of the intracystic or pericystic space with a scolicidal agent is often employed to prevent the emergence of recurrent hydatidosis as a consequence of these complications.

Povidone-iodine (polyvinylpyrrolidone-iodine, PVP-I) is a local antiseptic with activity against a wide spectrum of microorganisms[1], including protoscolices, as revealed by an *in vitro* trial[2]. Prophylactic peritoneal lavage with PVP-I solution has been demonstrated to be an effective and safe measure against intra-abdominal infections in animals, as well as in humans[3–6]. The effect of intraperitoneal PVP-I on experimental peritoneal hydatidosis was investigated in this study.

Materials and methods

Seventy-five albino rats, 3 months old, randomly selected from a population of rats bred under similar conditions, were used in this study. All of the manipulations described below were performed with strict compliance to antiseptic principles. The rats were subjected to a median laparotomy of 2 cm length performed with a scalpel under ether anaesthesia; the peritoneum was exposed and opened to reach the intraperitoneal cavity, in which 1 ml concentrated hydatid 'sand' was instilled with a pipette. All rats received samples of a single concentrate of hydatid sand, which was prepared from the fresh hepatic hydatid cysts of sheep by collecting cyst fluid into a glass container and allowing it to stand for 10 min at 37°C, after which the supernatant was discarded. The remaining sediment (hydatid sand) contained approximately 15 000 scolices/ml, which were 95 per cent viable immediately before inoculation as determined from their motility characteristics under the light microscope. Two minutes after the inoculation of scolices, the rats were randomly divided into three equal groups identified as the PVP-I, control and hypertonic saline (HS) groups. They were put into three separate compartments bearing different code numbers, where they remained for the rest of the study. Using an injector, 10 ml of one of three solutions was instilled into the peritoneal cavity of each rat; the PVP-I group received a mixture containing 1 ml 10 per cent PVP-I solution and 9 ml Ringer's lactate solution (final solution of 1 per cent PVP-I, free iodine concentration 1 ppm)[7]. The HS and control groups received 20 per cent saline and Ringer's lactate, respectively. All workers participating in the subsequent steps of the investigation were ignorant of how each rat had been treated. Two minutes later, 4 ml of the excess fluid in the lower part of the abdominal cavity was gently aspirated with an injector to facilitate the closure of the laparotomy incision with a continuous subcuticular 4/0 polyglactin suture. None of the rats received any medication before or after this operation. The rats were kept under continuous observation in identical maintenance conditions. Four months later, the surviving rats were killed under ether anaesthesia and a second laparotomy was performed. The intermesenteric areas and all peritoneal surfaces were examined with the aid of a dissection microscope to determine the number of hydatid cysts.

Statistical analysis

All data were entered into a computerized database (Works DataBase, Productivity Software Incorporated, Boston, USA) in the form of three sets of results designated by the previously assigned code numbers. Data were generally expressed as the mean (s.e.m.). Statistical analyses were realized with the StatView package (BrainPower Incorporated, California, USA) and consisted of Student's t and Fisher's χ^2 tests. A P value $<0{\cdot}05$ was accepted as significant. The results were decoded after the statistical analyses were completed.

Results

No statistically relevant difference was encountered in the weight, age and sex ratio of the groups. Two rats from the PVP-I, five from the HS and three from the control group died in the early postoperative period, presumably because of anaesthetic complications. Sixty-five rats survived without weight loss, general deterioration or impaired wound healing and were killed 4 months later. The differences in the survival rates of the PVP-I, HS and control groups were not significant (*Table 1*). The percentage of rats with at least one hydatid cyst was 90·9 per cent in the control group, this was moderately reduced to 50 per cent in the HS group, but showed a striking decrease to 8·7 per cent in the PVP-I group. The mean number of cysts per animal also displayed a statistically significant reduction in the PVP-I group, as compared with the other two groups. The ratio of rats with more than 10 cysts to rats with 0–10 cysts was higher in the control group, in contrast to the PVP-I and HS groups, which had comparable results.

Discussion

Surgical intervention remains the primary mode of treatment for hydatid disease. The various surgical methods employed

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Table 1 *Findings at the end of the trial*

	Povidone-iodine group	Hypertonic saline group	Control group
Surviving rats (*n*)	23	20	22
Survival rate (%)	92	80	88
Weight (g) (mean(s.e.m.))	172(6)	170(4)	165(6)
Male female ratio	13 10	12.8	13.9
Rats with hydatid disease (%)	8·7†	50*	90·9
No. with >10 cysts/0–10 cysts	1/22‡	5/15‡	20/2
No. of cysts per rat (mean(s.e.m.))	0·6(0·5)†	4·7(1·4)*	23·3(2·5)

* $P \leqslant 0{\cdot}01$ *versus* control group, † $P \leqslant 0{\cdot}01$ *versus* hypertonic saline group and $P \leqslant 0{\cdot}001$ *versus* control group (Student's *t* test); ‡ $P \leqslant 0{\cdot}01$ *versus* control group (Fisher's χ^2 test)

for the treatment of hydatid cysts[8–14] can be classified into two basic alternatives: resection and evacuation. Resection is obviously more desirable but is often not technically feasible, and evacuation combined with scolicidal irrigation of the intracystic or pericystic space has to be preferred[9]. Formaldehyde[12], hypertonic saline[8–11], silver nitrate[13,14], cetrimide[9] and other solutions have been used as scolicidal agents, but most have unacceptable side-effects[15–18] limiting their use. None of these agents can be safely employed for intraperitoneal irrigation.

PVP-I is a synthetic polymer of *N*-vinylpyrrolidone strongly complexed to iodine. It is devoid of the problems inherent in the use of free iodine, such as serious toxicity to tissues as well as instability and insolubility in water, while retaining and enhancing its microbicidal properties[1]. The following discussion refers to the solution form of PVP-I.

Although the beneficial effects of intraperitoneal PVP-I in the prevention of experimental peritonitis were reported quite early[3–5], the use of this route of administration in humans was late to follow owing to concerns about its possible systemic, especially renal, iodine-related toxicity or interference with wound healing suggested by some workers[19,20]. Interest in using intraperitoneal PVP-I to treat peritonitis and prevent postoperative intra-abdominal bacterial infections has revived recently with the development of PVP-I solutions containing PVP polymers of relatively homogeneous and lower molecular weights as compared with the formerly used preparations. This change has proved to be extremely important as it is associated with the rapid renal clearance of polymers, making it possible to avoid their storage in solid organs[1,21]. In the randomized, saline-controlled human trial of Sindelar *et al.*[6], intraperitoneal irrigation with low molecular weight 1 per cent PVP-I solution during contaminated abdominal procedures led to a significant decrease of postoperative intra-abdominal infectious complications; evidence of local or systemic iodine toxicity or impairment of wound healing was not reported.

Our results show that PVP-I has potent *in vivo* scolidical activity which is of prophylactic value against secondary peritoneal hydatidosis and is superior to hypertonic saline used for the same purpose Evacuation combined with irrigation of the intracystic and/or pericystic space with PVP-I can be regarded as an effective method for the surgical treatment of hydatid cysts We suggest a 1 per cent solution because it has an attendant free iodine level[7] of only 1 ppm, is not associated with the adverse effects of higher concentrations[22], and has been previously used for intraperitoneal irrigation without significant harm in humans[6].

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Topical application of honey in treatment of burns

M. Subrahmanyam

Department of Surgery, Dr V. M. Medical College, Solapur 413 003, Maharashtra, India

Correspondence to.
Dr M. Subrahmanyam

A total of 104 cases of superficial burn injury were studied to assess the efficiency of honey as a dressing in comparison with silver sulfadiazine gauze dressing. In the 52 patients treated with honey, 91 per cent of wounds were rendered sterile within 7 days. In the 52 patients treated with silver sulfadiazine, 7 per cent showed control of infection within 7 days. Healthy granulation tissue was observed earlier in patients treated with honey (mean 7·4 versus *13·4 days). Of the wounds treated with honey 87 per cent healed within 15 days as against 10 per cent in the control group. Relief of pain, a lower incidence of hypertrophic scar and postburn contracture, low cost and easy availability make honey an ideal dressing in the treatment of burns.*

Infection continues to be an important problem in the treatment of burns To reduce bacterial growth under the burn surface, various agents such as silver sulfadiazine[1], 5 per cent silver nitrate[2], and Sulfamylon® (Winthrop Laboratories, Guildford, UK)[3] have been used and various methods of grafting have been tried[4–7]. However, none of the above approaches has eliminated the problem of infection.

Honey has been used as an adjuvant method of accelerating wound healing from ancient times and has been sporadically used in burns[8–10] The present study investigates its use in the treatment of burn patients

Patients and methods

A total of 104 cases of superficial thermal burns involving less than 40 per cent of the body surface were treated over the period July 1988 to December 1989 in our unit A detailed history was obtained regarding the mode of injury. A thorough physical examination was performed with emphasis on the type and extent of burns The cases were allotted at random to two groups The extent of injury in both groups varied from 5 to 40 per cent The general management of these patients remained the same in both groups, but group 1 (52 patients) was treated with pure, unprocessed, undiluted honey obtained from hives, after the wounds had first been cleaned with normal saline An application of 15–30 ml honey was made to the surface of the burn depending on its size After spreading the honey was covered with dry sterile gauze and bandaged Honey was applied daily and at the time of dressing the amount of discharge, foul smell, slough, type of granulation tissue, oedema of the surrounding area and signs of healing were noted Subjective factors such as relief of pain and local irritation were also noted.

In group 2 (52 patients) the wounds were covered with silver sulfadiazine impregnated gauze pieces which were replaced every day In both groups culture and sensitivity determinations were performed on swabs taken from the surface at the time of admission This was repeated on days 7 and 21 in all cases or until the wound healed The time required for complete healing was noted in both groups Data were analysed using the χ^2 test

Results

Of the 104 patients with burns, 82 were males and 22 females. The youngest patient was 1 year old and the oldest was 65 years. Seventy patients were in the age group of 21–30 years and, of these, 30 patients in group 1 and 31 patients in group 2 had burns of between 21 and 40 per cent *Table 1* shows the age, sex

Table 1 *Age, sex and extent of burns in 104 patients*

	Number of patients in age groups in years											
	1–10		11–20		21–30		31–40		41–50		51–65	
Extent of burns (%)	M	F	M	F	M	F	M	F	M	F	M	F
Group 1 – patients treated with honey (*n* = 52)												
0–10	1	0	1	0	2	1	1	0	0	0	0	0
11–20	0	0	0	0	1	2	0	1	0	0	1	0
21–30	0	0	1	0	16	1	1	0	2	1	1	1
31–40	0	1	0	1	12	1	1	0	1	0	0	0
Total	1	1	2	1	31	5	3	1	3	1	2	1
Group 2 – patients treated with silver sulfadiazine (*n* = 52)												
0–10	1	1	1	0	0	1	0	0	0	0	0	0
11–20	1	0	1	1	1	1	1	1	1	1	1	0
21–30	1	0	0	0	17	1	1	0	0	1	0	1
31–40	0	0	1	0	11	2	0	1	1	0	0	0
Total	3	1	3	1	29	5	2	2	2	2	1	1

M, male, F, female

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Table 2 *Time required for healing in patients with burns*

Time required for healing (days)	Group 1 (patients treated with honey)	Group 2 (patients treated with silver sulfadiazine)
0–10	33	3
11–15	12	2
16–20	5	17
21–30	1	18
31–40	1	7
41–50	0	4
51–60	0	1
Total	52	52

and extent of burns in both groups; 84 patients attended the hospital within 6 h of injury, whereas 20 patients attended later.

In patients treated with honey, healthy granulations appeared in the majority of cases after about 1 week (mean 7·4 days). The wounds healed in 33 patients within 10 days, and in 11–15 days in 12 patients. In patients treated with silver sulfadiazine, healthy granulation appeared later (mean 13·4 days) and 16–30 days were required in 35 cases for wound healing (*Table 2*). The time taken for wound healing differed significantly between the groups ($P<0{\cdot}001$). In patients in group 1, 43 showed positive swab cultures at the time of admission and in nine patients the swab culture was sterile. Of the 43 swab culture positive patients, 39 (91 per cent) were rendered sterile after treatment with honey for 7 days and four cases showed persistent infection In group 2, 41 of the 52 patients had positive swab cultures at the time of admission and in 11 patients the swab was sterile Of the 41 who had positive swab cultures, only three became sterile after 1 week and 38 had persistent infection ($P<0{\cdot}001$). The organisms isolated in 84 positive swab cultures in both the groups were *Staphylococcus aureus* coagulase positive (14), streptococci (14), *Escherichia coli* (13), *Pseudomonas* (9), *Klebsiella* (15), *Citrobactor* (10) and *Proteus* (9).

In patients treated with honey, one patient had hypergranulation and required cauterization and one case had postburn contracture. It was our impression that these patients had more relief of pain and less irritation. Allergy or other side effects were not observed. Patients treated with silver sulfadiazine had hypergranulation in three instances and postburn contracture and hypertrophic scar in six and seven cases respectively.

Discussion

Honey consists of simple sugars and is an excellent source of energy. It is itself sterile and inhibits the growth of both Gram-negative and Gram-positive organisms[11–13]. Its antimicrobial properties are attributed to its low pH (3 6), a thermolabile substance called inhibine[13,14] and its hygroscopic properties The viscous barrier to wound invasion by micro-organisms and fluid loss are important factors in rendering the burn wounds sterile and preventing colonization. Honey also contains enzymes such as catalase which may aid the healing process[15]. The acceleration of epithelialization in our study appeared to occur between 6 and 9 days. The chemical debridement action of honey, removal of offensive smell, and energy source provision of honey in a catabolic situation may also help the process of healing. Isolated reports of use of honey in decubitus ulcer, infected wounds, burns and open wounds following radical vulvectomy have also appeared[16–18]

The present prospective study has shown that the healing properties of honey helped burn wounds to heal earlier and with fewer complications than conventional treatment.

Acknowledgements

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Surgical workshop

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Carbon dioxide insufflation in gastrointestinal surgery

J. Cabrol, C. Griffiths and J. Alexander-Williams

Department of Surgery, The General Hospital, Birmingham B4 6NH, UK
Correspondence to: Professor J. Alexander-Williams

Patients who have had peritonitis or many previous operations often have multiple dense adhesions. When they need a further laparotomy the dissection of these adhesions can be difficult, time consuming and small perforations of the bowel may not be recognized[1]. In an attempt to minimize this problem we developed a technique of carbon dioxide insufflation of the small bowel to identify such leaks.

Technique

When multiple small bowel adhesions are expected or encountered during laparotomy, a size 16 Fr nasogastric tube is passed into the stomach by the anaesthetist and, wherever possible, its position is checked manually. It is connected to an automatic carbon dioxide insufflator, as used to induce pneumoperitoneum for laparoscopy. Sufficient carbon dioxide is introduced to distend the stomach (1 to 2 litres) and, when possible, the gas is assisted through the pylorus by pressing the gastric gas to the patient's right. Metoclopamide injected intravenously has been tried but was less effective than manual compression of the stomach. Once the gas enters the proximal jejunum it is milked along the bowel towards the caecum.

As the gas traverses the bowel any perforation is easily detected by an audible and visible gas leak and may be confirmed if the examination is performed with the bowel distended under normal saline. Any defects in the bowel wall may then be repaired by suture and rechecked. Anastomoses in the stomach and the duodenum may similarly be tested to check they are gas-tight.

The carbon dioxide is gradually absorbed by the bowel over 10 min and any residual gas within the stomach is withdrawn via the nasogastric tube.

Results

In the past 5 years the technique has been used in 98 laparotomies patients with multiple dense adhesions; the majority with Crohn's disease. Although the technique has only detected three major and four minor leaks, not otherwise obvious at operation, we have experienced no further patients who developed a fistula from apparently uninvolved bowel. In the series 19 suture lines have been demonstrated to leak gas and have been reinforced with extra sutures until gas-tight. Our impression is that another major benefit of the technique is the facilitation of the dissection of matted loops. Distention of the gut enables the plane of cleavage to be detected and divided easily in almost every case. It has never made dissection more difficult. We have encountered no difficulty in abdominal wall closure from distended gut. The expired carbon dioxide concentration is monitored by the anaesthetist. The usual basal concentration of 3·5 to 3·9 kPA rises from 4·0 to 4·5 kPA for 5–10 min after introduction of the bolus.

Discussion

Carbon dioxide has been used frequently to distend the large intestine during colonoscopy, polypectomy and in double contrast barium studies[2-4]. It appears to have no ill effects with the expired carbon dioxide rarely exceeding the normal range of 3·5 to 4·5 kPA. Air insufflation is often used to test stapled low rectal anastomoses. Carbon dioxide has advantages as, unlike air, it is unable to support combustion and is more rapidly absorbed from the bowel than is air. Some questions still need to be answered such as: how does carbon dioxide affect patients with chronic pulmonary disorder and how does carbon dioxide affect patients with chronic intestinal ischaemia? Brandt *et al.*[5] showed that the arterial partial pressure of carbon dioxide did not change while intraluminal colonic pressure was maintained with carbon dioxide, confirming Roger's[2] observations that there is no contraindication to the use of carbon dioxide during colonoscopy, even in patients with obstructive airways disease[2]. Carbon dioxide has been observed to have a vasodilator effect in the cerebral, renal, coronary and peripheral vessels[6]. Brandt *et al.*[5] also showed that carbon dioxide increased colonic blood flow in dogs up to 5 kPA levels of intraluminal pressure. This effect of increasing colonic blood flow was also observed when a constant intraluminal pressure of carbon dioxide of 8–10 kPA was maintained; a pressure that we have never exceeded in the small bowel after insufflation of carbon dioxide. This supports previous studies, both *in vivo* and *in vitro*, which showed increases in arterial and venous blood flow, attributable to vasodilation, after perfusion of segments of small bowel with blood containing excess of carbon dioxide[7].

We suggest that the gut inflation technique using carbon dioxide is safe and useful in aiding separation of matted gut adhesions and in testing the integrity of the traumatized gastrointestinal tract and its anastomoses.

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Short note

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Radiological examination of failure of intravenous infusions

G. B. H. Lewis and J. F. Hecker

Department of Physiology, The University of New England, Armidale, New South Wales, Australia 2351
Correspondence to: Dr G. B. H. Lewis, Armidale and New England Hospital, Armidale, New South Wales, Australia 2350

Many patients experience problems with intravenous infusions. Phlebitis is the most common cause of infusion failure and has been the subject of numerous studies[1] but comparatively little is known about the next most common cause, extravasation. Except for one paper in which biopsies were taken[2], there is little information on what actually occurs when infusions fail in humans. In this paper, we present the results of a series of radiographs taken when infusions failed.

Patients and methods

Informed consent was obtained from 11 adult patients (including one of us (G.B.H.L.)) receiving intravenous infusions which had been diagnosed as 'tissued' or phlebitic by registered nurses (*Table 1*). Swelling and tenderness at the infusion site together with slowing of infusions were noted. All had 18 or 21 gauge Terumo® cannulas. Before the cannulas were removed, an occluding cuff was applied proximal to the infusion site to retain media and then one or more radiographs were taken after the injection of small amounts of Angiografin® contrast medium (total less than 2 ml). Ethical committee approval had been given.

It was the practice in the hospital not to resite infusions at fixed intervals but to monitor them carefully and resite when necessary.

Results

Three of the infusions had extravasated (*Table 2*). One (No. 9) was in an antecubital vein and the leakage of dye occurred through the vein wall at the cannula tip which was located at the elbow (*Figure 1*). Nursing staff had reported that the patient had repeatedly flexed the forearm before the extravasation occurred. With the two other extravasated sites, the contrast media initially filled the cannula and vein to a point past the tip and then passed back over the outer surface of the cannula to extravasate from the vein through the hole made by insertion of the cannula. There were filling defects in the vein in the 1 cm length past the cannula tip (*Figure 2*). A second injection in one of these (No. 5) cleared an obstruction at about 1 cm past the tip and the contrast medium then flowed into normal vein whereas in another (No. 6) a tributary had opened to allow some dye to escape.

Table 1 *Details of patient age and sex and infusion sites*

No.	Age (years)	Sex	Site	Time (h)	Intravenous fluids and drugs
1	38	M	Head	42	4% Dextrose + N/5 saline, ampicillin
2	52	M	Wrist	52	Hartmann's, 4% dextrose + N/5 saline
3	40	F	Wrist	74	4% Dextrose + N/5 saline, gentamicin, cefoxitin
4	79	F	Wrist	62	Hartmann's
5	78	F	Forearm	119	4% Dextrose + N/5 saline
6	62	M	Forearm	168	Hartmann's, 4% dextrose + N/5 saline, ampicillin, gentamicin
7	70	M	Forearm	44	4% Dextrose + N/5 saline, gentamicin, cephalothin
8	39	F	Forearm	28	Hartmann's, gentamicin
9	70	M	Elbow	71	Blood, normal saline
10	33	F	Elbow	26	4% Dextrose + N/5 saline
11	87	F	Elbow	21	Hartmann's, normal saline

There was no extravasation of dye in the other eight infusions but there was evidence of filling defects proximal to the tip of each (*Figure 3*). In two, dye entered the vein to a point a short distance past the cannula tip and then flowed back to enter a collateral vessel which joined the vein part way along the cannula shaft. Another showed a thread-like lumen from the cannula tip to a point near where the first side branch joined the vein while in three others there was a short length of constriction proximal to the cannula tip. There was usually

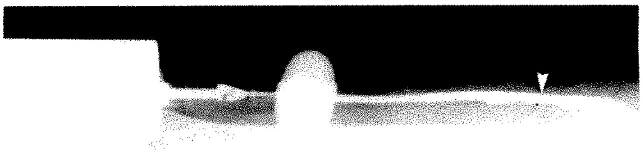

Figure 1 *Leakage of contrast media through the hole made when the cannula was inserted into the vein (No. 5). Note the filling defects proximal to the cannula tip. Media stopped in the first two radiographs (at the arrow) but a third injection cleared the blockage*

Table 2 *Findings when radiographs were taken of failed infusions before cannulas were removed*

Distances are from the cannula tip

1. Vein dilated except for 2 mm constriction just beyond the tip. Dye flowed back around the cannula to a valve but remained in the vein.
2. Short constriction 7 mm from tip. No filling defects.
3. Narrowing and irregularities just proximal to tip.
4. Vein thread-like with irregularities from tip to a collateral vessel (*Figure 3*)
5. Dye passed proximally for 15 mm to an obstruction and then distally along cannula before extravasating at the cannula entry site. A second injection cleared the obstruction and showed marked filling defects (*Figure 1*).
6. Vein constricted with filling defects partially obstructing flow. Some dye extravasated at cannula entry and also flowed back up a side branch to then pass along another vein.
7. Vein occluded proximal to tip. Dye passed back along cannula into a branch starting half way along the cannula and distally for 30 mm before passing proximally (*Figure 4*).
8. Infusion was slow and then stopped. Induration and slight tenderness around cannula. The initial resistance to dye injection disappeared. Radiograph showed slight constriction with small filling defects 5 mm past tip and then dilated vein. Probably a thrombus was dislodged by the dye.
9. Dye leaked at cannula tip at distal end of humerus (*Figure 2*).
10. Irregularity and partial filling defect for 10 mm from tip but no marked constriction. Dye had also flowed distally for several cm.
11. Veins small. Irregularities and a blockage 10 mm from tip. Dye then passed back along the cannula and finally proximally along a collateral.

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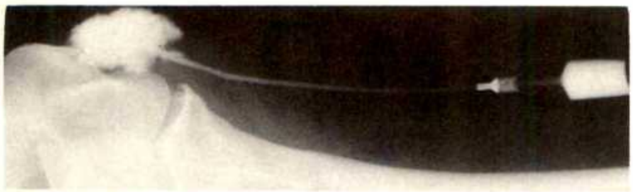

Figure 2 *An extravasated infusion (No. 9) at the cubital fossa with the leakage at the cannula tip*

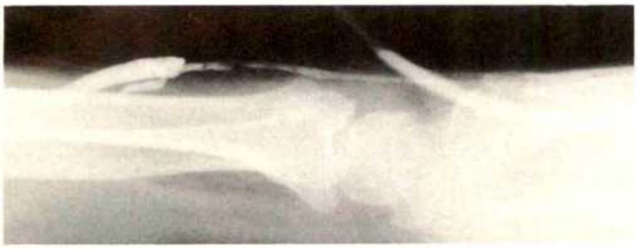

Figure 3 *A typical phlebitic vein (No. 4) with filling defects to near the junction with a side branch*

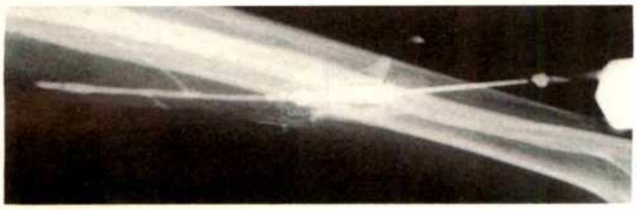

Figure 4 *An occluded vein (No. 7) with dye passing back and along a side branch*

irregular filling proximal to the cannula indicating thrombus formation which reduced the functional lumen of the vein.

Veins appeared normal after they were joined by a side branch.

Discussion

The reason why extravasation has been little studied is probably the widely held belief that it is caused by the intravenous cannula either pulling out of the vein or its tip piercing the vein wall. As a consequence, little is done to prevent extravasation except to immobilize the cannula. We have proposed that extravasation usually is a variant of phlebitis and occurs with leakage through the hole made where the cannula enters the vein[3]. For this to occur, flow proximal to the cannula tip must be obstructed and valves distal to the tip must close so that a high intraluminal pressure develops in the vicinity of the cannula tip. The similarity in rates at which phlebitis and extravasation develop[4] and the fact that local vasodilation reduces the incidence of both[5] support this hypothesis.

One infusion extravasated because the cannula tip had pierced the vein wall. The site of this infusion near the elbow and the fact that the patient had been moving this joint were consistent with the cannula tip piercing the vein wall. The other two extravasated with leakage occurring at the hole made where the cannula entered the vein[3]. For leakage to occur here, the vein must have occluded proximal to the cannula tip and valves distal to the cannula closed to stop blood flow. Bags of infusion fluid are usually about 150 cm above the bed and so the pressure in the vein in the region of the cannula would then be in the order of 110 mmHg or systolic pressure. It is common for nurses who find that an infusion has stopped to try to 'clear the line' by procedures such as pinching the infusion set tubing, winding it around a pen or flushing the cannula. These procedures will produce a momentary very high pressure at the cannula tip and may clear a blockage (as dye injection did in No. 5 and possibly in No. 8) but alternatively may dilate the hole in the vein wall made by the cannula allowing the fluid to extravasate (as in No. 5 and No. 6).

Extravasation may sometimes occur by the cannula being dislodged from the vein wall or puncturing it (No. 9). Puncturing of the wall is more likely with needles than with cannulas and this may explain why the ratio of extravasated to phlebitic infusions was higher with the former in the study of Tully *et al.*[6].

The nursing staff diagnosed one of the infusions (No. 8) as having extravasated and stopped the infusion but left the cannula *in situ*. Swelling was minimal when seen by one of us (G.B.H.L.) 6 h later when the main signs of tenderness and warmth indicated phlebitis. We have seen several sites which initially were tender and swollen with extravasated fluid. The infusions were stopped and the swelling disappeared in a few hours as the extravasated fluid was reabsorbed leaving sore and thickened veins which would then be diagnosed as phlebitic.

It is rarely documented but can usually be observed that the drip rate slows while phlebitis develops and the drip set regulator has to be slackened at intervals to maintain delivery. The resistance of normal veins to flow of blood and infusate is negligible but the narrowed lumens of these phlebitic veins would provide marked resistance to flow of infusate and explain why the drip rate usually slows before phlebitis becomes obvious.

Common crystalloid solutions are mildly acid with pH values of 4·3 or lower for dextrose solutions[7,8]. Such acidity would irritate the vein[3] and induce venoconstriction[9] which would lead to phlebitis or extravasation. Most phlebitic radiographs showed normal veins proximal to where a side branch joined which indicates that blood flowing through the side branch was able to neutralize the acidity and so reduce the irritation. Similarly, an increased blood flow resulting from local application of transcutaneous glyceryl trinitrate is likely to be the reason why this drug reduced threefold the incidences of both extravasation and phlebitis[5].

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New water-jet dissector: initial experience in hepatic surgery

H. U. Baer, G. J. Maddern and L. H. Blumgart

Department of Visceral and Transplantation Surgery, Inselspital, University of Berne, Berne, Switzerland

Correspondence to: Dr H. U. Baer, Klinik für Viszerale und Transplantationschirurgie, Inselspital, 3010 Bern, Switzerland

New approaches to hepatic resection have involved the introduction of water jets to disrupt liver parenchyma and expose vessels. The characteristics of current machines are shown in *Table 1*; they all suffer from the defect of employing low pressure water jets with consequent impaired efficiency. We have developed a high pressure, high velocity water jet instrument (*Figure 1*) which offers a range of advantages over earlier equipment (*Table 1*).

Surgical technique

The instrument consists of a hydrodynamic device for the elimination of parenchymal tissue so as to expose vascular and ductal structures. The system comprises a pressurized liquid source feeding via a flexible hose to a handpiece from which a fine nozzle extends. The nozzle has a diameter of either 20 or 70 μm. Water or saline is delivered at a pressure of 200–1000 bar allowing the stream flowing from the nozzle to have an initial velocity of at least 300 m s^{-1} (*Figure 2*). This high velocity jet increases in diameter as the distance from the tube increases. The jet stream is coherent for 30 mm from the tube tip and then radiates forming microdroplets and finally a spray of water at a distance of 40–80 cm from the tip of the tube (*Figure 3a*).

During operation the tip of the tube is advanced from a distance of about 40 cm towards the surface to be cut. As the beam approaches, increasing pressure is applied causing disruption as the force of the jet becomes greater. This is different from other water jets that produce a coherent beam over about 100 mm (*Figure 3b*) with the pressure applied being altered only by adjustment of the pumping system.

During dissection of the parenchyma, as vascular structures become evident, the instrument is withdrawn. To and fro movements of the hand cause a variation in the intensity of the jet which allows cleaning of vascular and ductal structures. Little experience is needed to allow effective use of the instrument. Once vessels are exposed they are either electrocoagulated, clipped or divided and ligated. Visibility in the operating field is excellent since the water jet washes away blood and parenchymal debris and the microdroplets remove air bubbles effectively. This fine spray remains in the operative field and seems to add no additional risk to the surgeon or theatre staff.

Clinical application

There are a variety of clinical settings in which this machine mght prove useful but we have confined ourselves so far to hepatobiliary surgery and the system has been employed for eight major liver resections. For such resections initial control of the vessels supplying the area to be removed has been obtained at the hilus or within the umbilical fissure, and control of the hepatic veins, when possible, has been obtained by retrohepatic dissection of the inferior vena cava. Parenchymal transection followed initial incision of Glisson's capsule and the new machine was used either on its own for parenchymal dissection or in combination with a finger fracture technique.

The machine allowed rapid transection of the parenchyma with accurate display of intraparenchymal vascular and ductal structures. It was particularly helpful in defining the major veins draining the liver and especially in the definition of the right portal pedicle during extended left hepatectomy.

The mean time for routine right hepatic resection or left hepatic resection in this department is approximately 4 h and for extended left hepatectomy 5 h. The number of cases in which we have tried using the new technique is not sufficient for full

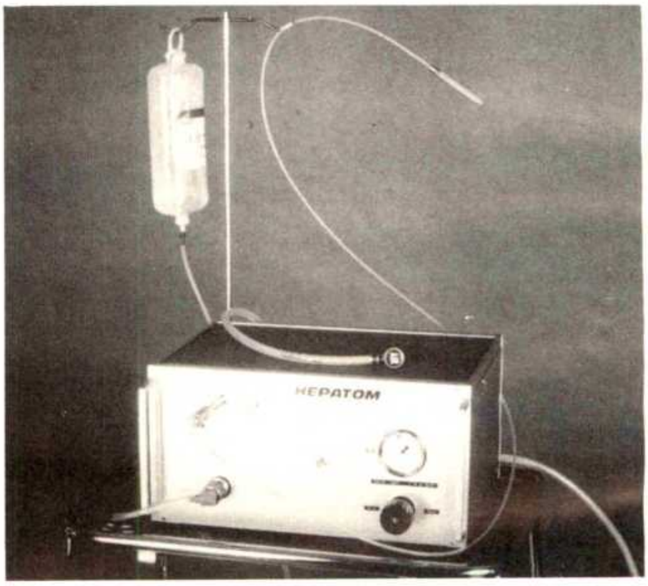

Figure 1 *Photograph of the assembled Hepatom dissector showing sterile water bag, pump, connecting tubing and nozzle. (ME Medical Exports AG, Berne, Switzerland)*

Table 1 *Comparison of different waterjet models*

Characteristics	LPS Persson*	LPS Uchino†	HPSS Baer‡
Diameter of nozzle (mm)	0·08–0·12	0·10–0·22	0·25–0·06
Pressure range (bar)	15–50	15–18	200–1000
Flow rate (ml s^{-1})	0·5–0·7	0·5–1·8	0·1–0·5
Kinetic energy at nozzle (W)	1·4	1·2	22
Distance of coherent jet stream (mm)	>100	>100	30
Option to alter jet form	No	No	Yes
Velocity of jet (m s^{-1})	80	47	>320
Formation of blood bubbles	Yes	Yes	No (destroyed by the high speed microdroplets)

LPS, low pressure system; HPSS, high pressure system; W, Watt; * Hellbergs Dental AB, † Sugino Machine Co. Ltd., ‡ ME Medical Exports AG

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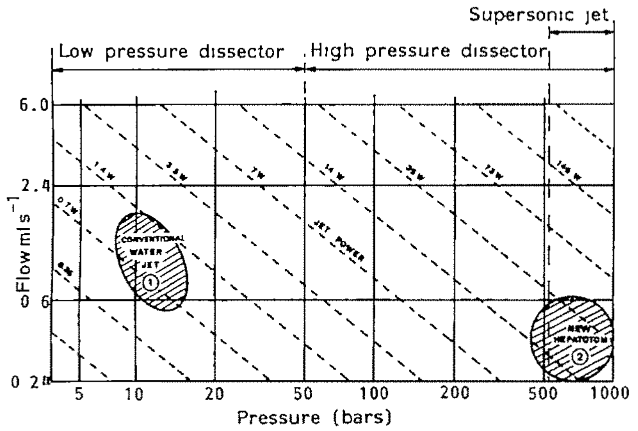

Figure 2 *The operating flow and pressure characteristics in which the conventional 1 and the new water-jet 2 (Hepatom) operate*

assessment but certainly there was not any prolongation of operating time. Blood loss for right or left hepatectomy or extended right hepatectomy using a finger fracture technique averages some 500 ml for operations in which the tumour does not encroach on major vessels of the hilus or the region of the vena cava, but it is somewhat higher for larger tumours in close proximity to these structures. The blood loss encountered during trial of the machine was within these limits, except for extended left hepatectomy for which we feel it was reduced and that operation was facilitated.

In four patients we have used the jet-dissector to create access for biliary–enteric anastomosis to intrahepatic bile ducts. The machine was used to expose an area of 3 cm^2 on the lower surface of the left lobe of liver within segment III It was found that the liver parenchyma could be gently washed away exposing a tree of peripheral branches of the segment III bile duct. It was possible to create a sufficiently wide and effective anastomosis (2 cm length) to a peripheral duct with minimal blood loss

Discussion

So far the instrument seems a valuable adjunct for the experienced surgeon in routine cases, and it is especially useful for major hepatic resection where only minimal clearance from major vessels can be achieved in the resection of large tumours. The machine is quick to use and the technique is easily learned We have been using the ultrasonic dissector for some time and find it useful but somewhat slow, difficult to manipulate and not effective with more fibrotic tissue

The water jet dissector offers a range of advantages The small outlet and specially designed nozzle produces a water jet which alters its pressure according to the distance from the tip of the nozzle. The flow of water is small, so that even in major extended hepatic resection the volume of liquid used is only 200–300 ml. The danger of absorption of fluid into the circulation is reduced. The speed of resection is almost the same as that of the finger fracture technique, and firm or even fibrous tissue can be dissected.

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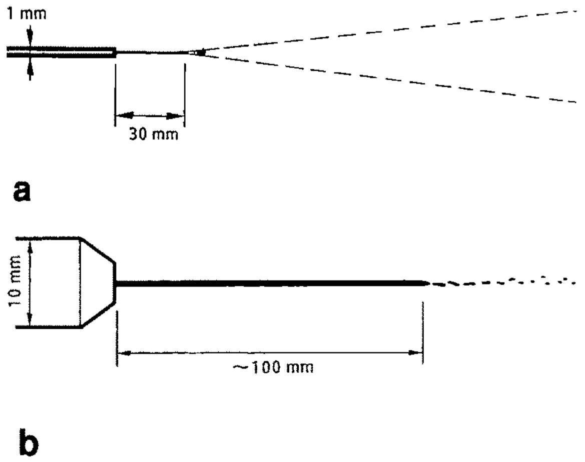

Figure 3 **a** *Diagrammatic representation of the new jet dissector stream characteristics, showing a divergent stream after 30 mm with microdroplet formation.* **b** *Diagrammatic representation of conventional jet stream characteristics, showing a coherent stream for 100 mm and subsequent droplet formation*

Correspondence

Potential hazards of mechanized surgical retractors

Sir

The letter by R J R Goodall (*Br J Surg* 1990, 77. 1195) regarding the safety of mechanized surgical retractors no doubt reflects genuine concern. However, an understanding of the electrical principles involved will no doubt dispel many of these fears.

The traditional, and essential, checks to ensure electrical isolation of the patient from the table are to prevent a point of contact which would earth the current. The concentration of current at such a point would be sufficient to cause tissue damage and coagulation. Indeed, we depend on this effect when we use the diathermy apparatus to coagulate or cut. However, when the current is diffused over a wider area, the damage is avoided, as is the case in the area covered by the diathermy plate. This is no doubt also true of the area of contact with mechanized retractors, an area which is increased if wet drapes intervene. If attempts are made to isolate the patient from the retractor, then the situation is as before, single small points of contact should be assiduously avoided.

I feel that extra emphasis should be placed on the fact that it is not electrical contact that matters, but electrical concentration. Surgeons who are considering acquiring these undoubtedly useful retractors should indeed consider the potential hazards carefully, but should be reassured that with a wide area of electrical contact, there is no significant risk.

R. O. Hart

Department of Surgery
Kidderminster General Hospital
Kidderminster DY11 6RJ
UK

Antiprotease therapy for acute pancreatitis

Sir

I read with interest the article by Wilson and Imrie (*Br J Surg* 1990; 77: 1252–5) concerning antiprotease therapy for acute pancreatitis. The authors demonstrate a significant survival advantage to rats given intraperitoneal fresh frozen plasma (FFP). They postulate that the $\alpha_2$macroglobulin (α_2M) content of FFP provided a therapeutic advantage over plasma protein fraction (PPF) or aprotonin and propose a clinical study. Such a study is likely to demand considerable quantities of fresh frozen plasma. This, however, is a scant resource which should perhaps best be reserved for the correction of life threatening coagulopathies. If only plasma protease inhibitors and α_2M in particular are needed for peritoneal instillation then a stable pooled plasma protein solution similar to PPF would seem ideal. Ironically in the preparation of PPF the Scottish protein fraction laboratory discards many kilograms of Cohn fractions II + III and IV-1 which are rich in α_2M and antiprotease activity[1]. A stable pooled plasma protein solution called silica gel fractionated plasma (SGF) has long been available in the USA[2,3]. SGF retains high levels of α_2M and significant antiprotease activity, which may explain its remarkable capacity to preserve organs for transplantation and prevent pancreatic reperfusion injury[4]. It would seem logical therefore to petition the supraregional protein fractionation laboratories of the UK to find ways of recouping α_2M containing plasma fractions to be available for this promising area of therapy in acute pancreatitis.

P. K. Donnelly

Department of Surgery
Leicester General Hospital
Leicester LE5 4PW
UK

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Irreducible inguinal hernia

Sir

The paper by Davies *et al* (*BR J Surg* 1990, 77. 1291–2) highlights several important points about the management of inguinal hernias in young children. However, we were surprised to read that as many as 16 per cent of their patients required emergency surgery.

During the past 18 months we have been referred 30 children under 2 years of age with irreducible inguinal hernias. Twenty-eight (93 per cent) were boys and 22 (73 per cent) were 6 months of age or younger. Approximately half the patients were referred from general practitioners, the remainder from district general hospitals or via the casualty department. All hernias were successfully reduced with a combination of parenteral sedation, elevation and careful taxis. No patient required emergency surgery, operative repair being carried out semielectively after 24–72 h.

In recent years there has been a gradual improvement in the published figures for successful non-operative reduction of irreducible inguinal hernias in children. Our experience concurs with that of Puri *et al*[1] who reported that 95.5 per cent of incarcerated inguinal hernias in infants could be reduced by taxis. Six of the 14 patients in the Southampton series had their hernias reduced under general anaesthesia with gentle taxis. Effective sedation beforehand might have avoided the need for emergency surgery with its attendant risks. These include both the hazards of general anaesthesia in infants[2] and the risks to the vas and vessels with the danger of testicular atrophy[1,3] during a potentially technically exacting operation. Intestinal infarction is uncommon[3] and if there are no obvious signs of strangulated bowel, gentle persistent taxis under sedation is worthwhile and should eliminate the need for emergency surgery in as many as 95 per cent of patients. Opiate sedation is permissible provided that the risks are understood and appropriate monitoring undertaken[4].

We strongly endorse the recommendation for rapid referral and early surgery for all infants with inguinal hernias.

M. D. Stringer
M. Higgins
S. N. J. Capps
S. J. K. Holmes

Department of Paediatric Surgery
Queen Mary's Hospital for Children
Carshalton SM5 4NR
UK

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Authors' reply

Sir

We thank Stringer *et al* for their kind comments. Their management of irreducible inguinal hernias is essentially the same as our own. We do use opiate sedation and will take up to 40 min of continuous taxis if required (as stated in the paper). The reason for a 16 per cent 'failure' of conservative management may be due to the late referral of children following onset of symptoms of strangulation (up to 96 h), and to the fact that many children (36 per cent) had had failed conservative management at other hospitals. We were able to reduce many of these but failed in some.

On a more optimistic note, a look through our audit computer shows no emergency operations were performed for irreducible inguinal hernias in the preceding 12 months. It appears the message is getting through.

N. Davis

Faculty of Medicine
University Surgical Unit
Southampton General Hospital
Southampton SO1 6HU
UK

Venous stasis and vein lumen changes during surgery

Sir

In a recent article by Coleridge-Smith *et al.* (*Br J Surg* 1990, 77. 1055–9) it was suggested that peroperative venous distension may be a factor associated with venous thromboembolism All patients were given a general anaesthetic (it seems) that then high resolution ultrasound imaging was used to measure the diameter of lower limb veins Their results revealed a significant distension of the gastrocnemius veins at the end of surgery with a loss of further distension with the leg in a dependent position. They postulate that the endothelium may be damaged by this distension thus increasing the likelihood of venous thromboembolism arising.

May I suggest that they have taken a large step between direct anatomical evidence of dilatation and its causal relationship with venous thrombosis They have ignored evidence suggesting that spinal and epidural anaesthesia probably reduces the incidence of deep venous thrombosis[1,2] in hip surgery Furthermore it has been shown using plethismography that calf blood flow and venous capacity are significantly higher 3 h after surgery in patients receiving epidural compared with general anaesthesia[3]

Surely it is impossible to relate structure in one plane to function as the original article has attempted Venous distension must be linked with flow which, after all, is probably the most important aspect of Virchow's triad. General anaesthesia using controlled ventilation will reduce venous return and increase venous distension whereas sympathetic blockade caused by spinal anaesthesia will cause venous dilatation and a compensatory increase in cardiac output and therefore blood flow

The proposition that venodistension is a true causal element in thromboembolic disease must at least compare increase in diameter with incidence of venous thrombosis for us to believe in its existence.

M. Hearn

Senior Registrar in Anaesthetics
Gloucestershire Royal Hospital
Gloucester GL1 3NN
UK

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Authors' reply

Sir

The evidence that venous distension (in the upper limb) is linked with an increased rate of deep venous thrombosis in the lower limb has already been established, and is referenced in our paper (Comerota AJ *et al.*, *Surgery* 1989, **106**. 301–9). The purpose of our study was to determine whether venous distension was present in the veins of the lower limb that may be affected by deep vein thrombosis A postoperative study to determine the relationship of venous distension in the lower limb with deep vein thrombosis is obviously the next stage This would be inappropriate unless we had a satisfactory method for estimating peroperative changes in vein diameter Our paper has established that the method used is capable of demonstrating peroperative distension in calf veins.

The suggestion that spinal and epidural anaesthesia reduces the incidence of deep vein thrombosis following hip surgery has not been substantiated by subsequent objective investigation[1], and it was not our purpose to investigate the effect of anaesthetic technique on the veins. Any difference these modalities of anaesthesia have compared with general anaesthetic techniques may be attributable to the direct pharmacological effects of local anaesthetic agents rather than an influence on blood flow, as the author cited by Dr Hearn acknowledges[2].

The measurement of diameter in one plane only was necessitated by the method of assessment employed, which we found less accurate in assessing the cross-sectional area of veins We made the assumption that a full vein would distend to approximately the same extent in both diameters, and since veins are not affected by atheroma we felt that this was not unreasonable Until recent months it has not been possible reliably to estimate the very low flow velocities in the lower limb veins studied using duplex ultrasound machines Internal filters in our machine removed the Doppler frequencies generated by slowly moving blood This has now been rectified and we anticipte the results of such measurements in the near future

We are not aware of evidence demonstrating that flow is the most important aspect of Virchow's triad, as suggested by Dr Hearn A classical study is to ligate a major vein (in an animal), under which circumstances it takes many hours for blood to clot What actually causes deep vein thrombosis to occur after surgical procedures remains unclear. Whilst the presence of prothrombotic changes in the blood as well as low flow rates in the veins have been established, alterations in the biochemical activity of the endothelium have not. What may matter is an alteration in shear rate in lower limb veins, which is a function of both flow rate and vessel diameter

P. D. Coleridge Smith
J. H. Scurr

Department of Surgery
University College and Middlesex School of Medicine
London W1N 8AA
UK

1. Fredin H, Rosberg H Anaesthetic techniques and thromboembolism in total hip arthroplasty. *Eur J Anaesthesiol* 1986, 3 273–81.
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Vacuum drainage of groin wounds after vascular surgery

Sir

We respond to points raised in the letter by Stansby *et al* (*Br J Surg* 1990; **77**. 1194–5) concerning our article on the use of vacuum drainage in groin wounds following vascular surgery (Dunlop *et al* *Br J Surg* 1990; **77**: 562–3) In this paper, we reported a randomized, blind, controlled trial of vacuum drainage after exploration of the femoral artery Within the confines of the trial protocol, we were unable to demonstrate any effect from the use of drains, and this has also been reported by other authors[1] Therefore, it is only rational to suggest that, since drains are uncomfortable for the patient, expensive and have not been shown to confer any benefit, their use should be discontinued Stansby *et al.* suggest this is not the case and argue that such drainage is still required, based on anecdotal evidence and speculation The multicentre trial, which Stansby *et al* suggest is required to assess the effect on graft infection rates, will have to report benefit before vacuum drains can be recommended

It is interesting to note that Stansy *et al* recommend that the drains be left in for more than 48 h despite their own reference[2] showing that 12 per cent of Redivac tips are already contaminated at 48 h and the demonstration by Watson *et al.* that contamination of drain tips was 7 per cent at 48 h, 33 per cent at 72 h and 50 per cent at 96 h after operation[3] We feel it is important that clinical practice should be based on sound data from objective evaluation and clinical trials, but it seems that not all surgeons share our view[1]

C. V. Ruckley
M. G. Dunlop
J. N. Fox
A. E. Clason
P. A. Stonebridge

Department of Surgery
The Royal Infirmary
Edinburgh EH3 9YW
UK

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Gallstone clearance: a randomized study of extracorporeal shock wave lithotripsy and chemical dissolution

Sir

Darzi *et al* incorrectly state in their recent article on gallstone clearance that 'it is not known whether gallstone fragments are cleared from the gallbladder without the use of oral dissolution therapy' (*Br J Surg* 1990; 77: 1265–7) The syndrome of the 'disappearing gallstone' is well recognized[1–4], and since the introduction of extracorporeal shock wave lithotripsy, workers have recovered fragments up to 8 mm in size from the stool within three days of treatment[5]

One might ask why, despite a treatment protocol allowing for up to 36 000 shocks, none of the ten lithotripsy alone patients had evidence of a stone-free gallbladder at 6 months This raises the question of the efficacy of their lithotripsy treatment

The authors conclude that gallstone clearance following lithotripsy appears to be dependent upon dissolution therapy That is not our experience. We have treated over 400 patients to date by lithotripsy alone, with favourable results when compared with those reported by other centres using adjuvant oral chemolitholysis[6]. We believe that the crucial factor for the success of lithotripsy is fragment size and we continue to treat patients until the largest remaining fragment is 3 mm or less. Gubernick *et al* have also found that, if stone fragments are smaller than 4 mm, lithotripsy can be equally successful without adjuvant bile salts[7] Recent analysis of our data has shown that patients who successfully clear gallstone fragments have significantly higher prelithotripsy gallbladder volume contraction measurements than those with residual fragments ($P = 0{\cdot}0033$)[8]

J. J. Donald
J. S. Fache
H. J. Burhenne

Department of Radiology
University of British Columbia and Vancouver General Hospital
855 W 12th Avenue
Vancouver BC
Canada V5Z 1M9

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Authors' reply

Sir

We have read with great interest the response to our paper[1]. This group doubt the role of oral dissolution therapy in gallstone fragment clearance following extracorporeal shock wave lithotripsy (ESWL). They argue that bile acid therapy is not required with gallstone lithotripsy on the basis that some gallstone fragments were found in the faeces of some patients undergoing gallstone lithotripsy[1] However, they totally disregard the largest randomized study to date which has clearly demonstrated that the combined lithotripsy and bile acid therapy is superior to lithotripsy alone[2]

They are also doubtful about the efficacy of our lithotripsy treatment but our results compare favourably to most centres treating patients with ESWL[3] However, we agree it might not compare favourably with this group's remarkable results where they have the highest clearance rates ever reported, not only using extended selection criteria but also treating patients without the use of bile acids therapy Their intensive treatment with lithotripsy and their excellent results have to be further applauded in view of the fact that other investigators have not been able to replicate these results using similar lithotripsy technology

A. Darzi
F. B. V. Keane

Department of Surgery
The Meath Hospital
Dublin 8
Ireland

1. Darzi A, Leahy A, O'Morain C, Tanner WA, Keane FBV Gallstone clearance: a randomized study of extracorporeal shock wave lithotripsy and chemical dissolution *Br J Surg* 1990; **77**: 1265–7.
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Gallbladder surgery following cholecystlithotripsy: suggested guidelines for treatment

Sir

We have read with great interest the article by Lee and Burhenne[1], in which they analysed the reasons for surgery in 23 patients who have undergone extracorporeal shockwave lithotripsy (ESWL) This study raises a number of important questions·

1 The authors fail to report their clearance rate in the 229 patients undergoing ESWL Although a figure of 61 per cent at 12 months has been mentioned in the discussion it refers to a subgroup of patients ($n = 136$) Surely, when analysing failures of a treatment, the success rate of the same treatment should be addressed when the objective of treatment is gallstone clearance.

2. There are two controversial points about ESWL The first of these refers to selection criteria In our experience using similar extended selection criteria, lithotripsy and dissolution therapy can be employed successfully but there is a price to pay, as the failure rate is as high as 17 per cent and the majority of these patients came to surgery[2,3] Assuming that failed clearance in symptomatic patients will require surgery we suggest that Lee and Burhenne's patients will require surgery with longer follow-up Again this goes back to knowing what their clearance rates were.

Secondly, we would like to address the need for bile acid therapy. In our experience the use of combined ESWL and bile acids therapy was significantly better than either treatment modality used alone[3]. The Dornier National Biliary Lithotripsy Study also confirms that the combined treatment was significantly better than lithotripsy alone[5] In the context of world experience with ESWL and/or dissolution therapy Lee and Burhenne's results would have to be regarded as remarkable.

3. The authors suggest that 16 of the 23 patients did not require surgery, in particular the 5 patients with acute pancreatitis and 11 patients with biliary pain. They argue that ESWL could be repeated when the acute pancreatitis has subsided and yet they exclude patients with acute pancreatitis from the lithotripsy programme.

In relation to biliary colic, whilst the physician might find it acceptable that 35–58 per cent of their patients will suffer from biliary pain during or after biliary lithotripsy, this situation might not be acceptable to patients, some of whom might prefer to undergo a surgical procedure We think it is probably wrong for physicians to accept these figures on behalf of their patients, whilst doggedly persisting with the philosophy of avoiding surgery at all costs

With regard to these comments, we feel the results of Lee and Burhenne have to be interpreted with caution

A. Darzi
F. B. V. Keane

Department of Surgery
The Meath Hospital
Dublin 8
Ireland

1. Lee SH, Burhenne HJ Gallbladder surgery following cholecystolithotripsy: suggested guidelines for treatment. *Br J Surg* 1990, **77**: 1268–71
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Authors' reply

Sir

We appreciate the opportunity to clarify the three questions for Drs Darzi and Keane regarding our article

1. The 61 per cent complete clearance rate of the gallbladder is indeed our published success rate. Like other investigators, we believe only a 12-month follow-up to lithotripsy to be meaningful. One hundred thirty-six patients were available from our institution for follow-up in October 1989[1]. They are included in the 229 patients evaluated later in our article for gallbladder surgery following cholecystlithotripsy, as cholecystectomy occurred obviously earlier than 12 months in the added patients

2. Publications from lithotripsy centres agree that selection restriction to single stones ≤30 mm will improve overall results. It is reasonable to assume that patients with failed lithotripsy will eventually come to surgery, but no long-term experience has been reported

Concerning the need for added bile acid therapy, Darzi and Keane refer to their experience randomizing lithotripsy alone, dissolution therapy alone, or combined therapy in a total of 35 patients[2]. None of the ten lithotripsy alone patients had evidence of a stone-free gallbladder at six months This complete failure of lithotripsy has not been reported by other investigators and one must raise the question of efficacy of the Dublin treatment with a piezoelectric lithotripter Results of the Dornier National Biliary Lithotripsy Study quoted by Darzi and Keane apply only within the restrictions of that particular protocol. Extracorporeal shockwave treatments were artibrarily limited to 1500 shocks, and less than half of the patients received a second treatment This was permitted only if stone fragments were >5 mm. Both of these studies utilized a full course of oral chemolitholysis but employed restricted shockwave lithotripsy. Darzi and Keane do not appear to be aware of the fact that when the largest single institution experience was analyzed in the Dornier Study, 'No significant difference was noted between the ursodeoxycholic acid and placebo groups'[3] Our experience has also been confirmed by Gubernick *et al.*[4] who found that if stone fragments were <4 mm, lithotripsy could be equally successful without adjuvant bile salts

3. We see no contraindication to our protocol if we retreat patients after pancreatitis has subsided. The Munich group has also dealt with five cases of pancreatitis following cholecystlithotripsy and four of these patients were managed successfully without further intervention[5] Darzi and Keane's interpretation of our publication is also erroneous if they believe that we 'as physicians accept a high incidence of biliary colic on behalf of our patients' We believe it is the patients' choice between surgery and lithotripsy, as long as they have been fully informed about success and complications

H. J. Burhenne
S. H. Lee

Department of Radiology
University of British Columbia and Vancouver General Hospital
855 W. 12th Avenue
Vancouver, B C.
Canada V5Z 1M9

1. Fache JS, Rawat B, Burhenne HJ. Extracorporeal cholecystlithotripsy without oral chemolitholysis *Radiology* 1990, **177** 719–21.
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Book reviews

Practical Gastrointestinal Endoscopy. 3rd edn.

P. B Cotton and C B Williams. 175 × 250 mm Pp 277 Illustrated 1990 Oxford Blackwell £27 50

I began to read the third edition of this very popular book whilst travelling by car to London. Like a good novel, I had finished reading it by the end of the return journey. The authors bring to their writing the clarity of expression, perception of other endoscopists' difficulties and the depth of their vast experience that is so evident when they are lecturing or teaching. There is little in the field of endoscopy that has not been done by this country's two foremost endoscopists and this book abounds with practical advice. It is lavishly illustrated with line drawings and there is much within it for both the experienced and the novitiate, doctor or nurse As usual, this third edition has been completely updated, with 14 chapters concerning all aspects of endoscopy. I found the sections on organizations of the endoscopy unit and the selection of video endoscopy or fibre endoscopy particularly interesting and useful. In the fourth edition I would hope to see some expansion of the sections relating to laser treatment and the authors will need to decide whether they should encompass endoscopic surgery and in particular laparoscopy

D. E. F. Tweedle

Withington Hospital
Manchester M20 8LR
UK

Textbook of Liver and Biliary Surgery

W C. Meyers, R. Scott Jones 250 × 260 mm Pp 512. Illustrated 1990 Philadelphia. Lippincott $99.50 hardback

The two co-authors of this book have produced a very readable account of their field written in a clear and succinct style.

The text is well laid out in 12 logical sections starting with anatomy and physiology and progressing through all areas of liver and biliary surgery The final chapter is an interesting account of hepatobiliary physiology and diseases in pregnancy The diagrams are good and the photomicrographs and radiographs are adequately reproduced, a high proportion being culled from other texts and books (with acknowledgements). Each chapter is comprehensively referenced and in addition there is an annotated listing of 'selected readings' There are two useful appendices listing normal laboratory values and drugs that induce hepatic necrosis or hepatitis.

I have one minor criticism, the index is not as comprehensive nor as reliable as it might be The entry for Caroli's disease for example indicates a brief mention in the chapter on liver cysts and omits the major discussion in the chapter on choledochal cysts

This book can be recommended to all trainees and also to more experienced surgeons who require an accessible account of topics in hepatic biliary surgery with a comprehensive and current bibliography

M. C. A. Puntis

Senior Lecturer in Surgery
University of Wales College of Medicine
Cardiff CF4 5XN
UK

Plastic and Reconstructive Breast Surgery (Vols. 1 and 2)

J Bostwick 220 × 285 mm. Pp 490 Illustrated. 1990 London William and Wilkins £320 00 hardback

This is rightly the bible of reconstructive breast surgery. Not only does it contain the current wisdom, but it also comes in two testaments! This is the second edition of John Bostwick's book; the first was published by another company and called *Aesthetic and Reconstructive Breast Surgery*. The second edition has been considerably expanded and is divided into *Fundamentals and Aesthetic Breast Surgery* (volume 1) and *Reconstructive Surgery* (volume 2) It is written by one of the very best plastic surgeons (and a good marathon runner) who has published extensively Many of his patients come from outside Atlanta and he is referred cases where the result from other centres has been less than satisfactory As such there is a useful chapter on what can go wrong in this sort of surgery and how to try and resolve these problems

There is an element of repetition in some sections and a few might quibble about the amount of space devoted to the patient as a whole, but these do not detract from the overall impression of a definitive text

The book is beautifully produced, eminently readable and should be on the shelf of any surgeon who carries out breast reconstruction It is expensive, but so are many of the finest things around us.

J. R. C. Sainsbury

Department of Surgery
Royal Infirmary
Huddersfield HD3 3EA
UK

Detection and Treatment of Early Breast Cancer

I. S. Fentiman. 250 × 190 mm Pp. 261. Illustrated. 1990 London Martin Dunitz. £49.95 hardback

This is an idiosyncratic book. It is claimed to be aimed to oncologists and surgeons treating breast cancer and is supposed to challenge the traditional methods of management and question accepted methods of diagnosis and screening It would be nice if one could report that it achieved this (especially one written by a surgeon) It is good to see a single author book, even if this does mean that the text is largely derived from references which appear to originate from one small area of London As such it provides a useful review of the status quo. I fear that many people whose first language is not English will find the book hard-going, sprinkled as it is with odd little asides and comments Those working in the field will probably look at a copy to see whether they like the style, but will probably wish to read more widely to achieve a balance

This is indeed an idiosyncratic book.

J. R. C. Sainsbury

Department of Surgery
Royal Infirmary
Huddersfield HD3 3EA
UK

Notices and announcements

20 April 1991
Rectum Carcinoma 1991
Ghent, Belgium
Information Dr D Claeys, Department of General Surgery, Algemeen Ziekenhuis Maria Middelares, Kortrijksesteenweg 1026, B-9000 Gent, Belgium

8–10 May 1991
Blood Vessel Imaging Using Ultrasound Techniques
Torquay, UK
Information Mr K. N Humphries, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK

8–11 May 1991
Melanoma '91, Brighton International Melanoma Conference
Brighton, UK
Information Dr N Kirkham, Department of Histopathology, Royal Sussex County Hospital, Brighton BN2 5BE, UK

8–11 May 1991
XXVIth Congress of the European Society for Surgical Research and the VIIIth Tripartate Meeting of The Surgical Research Society and The Society of University Surgeons
Salzburg, Austria
Information ESSR Congress Office, 1st Surgical Department, Landeskrankenanstalten, Mullner Hauptstrasse 48, A-5020 Salzburg, Austria

15–18 May 1991
82nd Annual Meeting of the American Association for Cancer Research
Houston, Texas, USA
Information American Association for Cancer Research, Public Ledger Building, Suite 816, Sixth and Chestnut Streets, Philadelphia, PA 19106, USA

17 May 1991
British Association for Endocrine Surgeons
Cambridge, UK
Information Mr A W Goode, Surgical Unit, 4th Floor Alex Wing, The Royal London, London E1 1BB, UK

20–22 May 1991
Trauma 91
Witwatersrand, South Africa
Information Gwen Watkins, Kennedy, Watkins & Associates, 27 Landau Terrace, Richmond 2092, South Africa

20–24 May 1991
Pacific Association of Paediatric Surgeons 24th Annual Meeting
Hong Kong
Information Secretariat, PAPS Hong Kong, Deparfment of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

24–25 May 1991
Surgical Infection Society – Europe, 4th Annual Meeting
Athens, Greece
Information Triaena Congress, 22–24 Harilaou Trikoupi Street, GR-106 79 Athens, Greece

24–25 May 1991
MedTech '91
Trondheim, Norway
Information Laser-Medizin-Zentrum GmbH, Koordinations Buro MedTech, Krahmerstr 6–10, 1000 Berlin 45, Germany

30 May–1 June 1991
4th International Symposium on the Biology, Immunology and Surgery of the Greater Omentum
The Netherlands
Information Secretariat, 4th International Omentum Symposium, Mrs W J Buys–Utrecht Cancer Research Centre, Servaasbolwerk 14, 3512 NK Utrecht, The Netherlands

June 1991
33rd Annual Meeting of the International College of Angiology
Singapore
Information International College of Angiology, 1044 Northern Blvd, Ste 103, Roslyn, New York 11576, USA

2–14 June 1991
Methods of Immunologic Research and Diagnosis
Buffalo, New York, USA
Information James F Mohn, Director, The Ernest Witebsky Center for Immunology, 272 Sherman Hall, Buffalo, New York 14214, USA

6–8 June 1991
5th European Congress of the Society for Surgery of the Shoulder and the Elbow
Wurzburg, FRG
Information Prof Dr med J Eulert, Orthpadische Universitatsklinik, Konig-Ludwig-Haus, Brettreichstr. 11, 8700 Wursburg, FRG

6–10 June 1991
American College of Cryosurgery 12th Annual Scientific Meeting
La Jolla, California, USA
Information American College of Cryosurgery, Attn Michael Thompson, PO Box 3116, Evanston, IL 60204-3116, USA

9–12 June 1991
Fifth International Conference on Malignant Lymphoma
Lugano, Switzerland
Information F Cavalli, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

19–22 June 1991
73rd Annual Meeting of The Endocrine Society
Washington, D C., USA
Information The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

11–13 July 1991
XVIth International Update on Liver Disease
London, UK
Information Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

12–13 July 1991
Hong Kong Surgical Forum
Hong Kong
Information Vera Fung, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

14–16 July 1991
Techniques in Pulmonary and Oesophageal Surgery
Liverpool, UK
Information Mr R J Donnell, Cardiothoracic Centre, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB, UK

25–31 August 1991
International Surgical Week
Stockholm, Sweden
Information Scientific Secretariat, 155, Hauptstrasse 63, PO Box 411, CH-4153, Reinach BL1, Switzerland

1–6 September 1991
6th World Congress in Ultrasound
Copenhagen, Denmark
Information Spadville Congress Service Sommervaj 3, DK-3100 Hornback, Denmark

4–6 September 1991
1st European Conference on Advances in Wound Management
Cardiff, UK
Information Christine Jones, Macmillan Conferences, 4 Little Essex Street, London WC2R 3LF, UK

7–10 October 1991
5th Congress of the European Society for Organ Transplantation
Maastricht, The Netherlands
Information 5th ESOT Congress, Conference Agency Limburg, University Hospital Limburg, PO Box 1918, 6201 BX Maastricht, The Netherlands

7–9 November 1991
3rd Combined Meeting of the Nederlandse Vereniging voor Thoraxchirurgie and the Deutsche Gesellschaft für Thorax-, Herz- und Gefässchirurgie
Maastricht, The Netherlands
Information Organizing Secretariat, Conference Agency Limburg, University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

17–23 November 1991
Surgery of the Pancreas, Liver and Biliary System
Edinburgh, UK
Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

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Announcement and call for papers

THE BREAST

A new quarterly international journal will be launched in Spring 1992

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J Michael Dixon
Senior Lecturer in Surgery
University Department of Surgery
Royal Infirmary of Edinburgh
Lauriston Place, Edinburgh EH3 9YW, UK

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